# DESCRIPTION

## EVALUATING METHOD, CALCULATING METHOD, EVALUATING APPARATUS, CALCULATING APPARATUS, EVALUATING PROGRAM, CALCULATING PROGRAM, RECORDING MEDIUM, EVALUATING SYSTEM, AND TERMINAL APPARATUS FOR FUTURE RISK OF DEVELOPING CEREBRAL AND CARDIOVASCULAR EVENTS

## TECHNICAL FIELD

[0001] The present invention relates to an evaluating method, a calculating method, an evaluating apparatus, a calculating apparatus, an evaluating program, a calculating program, a recording medium, an evaluating system, and a terminal apparatus for future risk of developing cerebral and cardiovascular events.

## BACKGROUND ART

[0002] Heart diseases, such as myocardial infarction, and brain diseases, such as cerebral infarction and cerebral hemorrhage, are the second and third leading causes of death in Japan. One of the primary causes of these diseases generally called cerebral and cardiovascular events are thought to be malfunction of blood vessels, such as arterial sclerosis, triggered by metabolic syndrome.

[0003] Early detection of the cause of disease resulting from metabolic syndrome and the like and intervention appropriate for the cause of disease are necessary to prevent cerebral and cardiovascular events. Utilization of biomarkers is considered to be useful to detect the cause of disease.

[0004] Amino acids, which play a key role in metabolic pathways among metabolites in living organisms, have attracted attention as biomarkers. Among metabolites,

amino acids are contained in large amounts in blood, and their physical properties are relatively similar to each other. Amino acids therefore have desirable properties to serve as biomarkers, for example, to enable precise analysis.

[0005] It has been reported that differences of plasma amino acid concentrations are a risk factor of future cerebral and cardiovascular events (Non Patent Literatures 1 to 4). As a prior patent, Patent Document 1 has been published, which relates to a method of evaluating a future state of cardiovascular events using amino acid concentrations in blood.

PRIOR ART REFERENCES

PATENT DOCUMENT

[0006] Patent Document 1: JP-A-2013-178238

NON PATENT LITERATURE

[0007] Non patent Literature 1: Ruiz-Canela M. et al. Clin. Chem. 2016, 62, 582-592

Non patent Literature 2: Shah SH. et al. Circ. Cardiovasc. Genet. 2010, 3, 207-214

Non patent Literature 3: Shah SH. et al. Am. Heart. J. 2012, 163, 844-850

Non patent Literature 4: Magnusson M. et al. 2013, Eur. Heart. J. 34, 198201989

DISCLOSURE OF INVENTION

PROBLEM TO BE SOLVED BY THE INVENTION

[0008] However, there has been a demand for further precision in development of determination techniques related to future risk of developing cerebral and cardiovascular events using blood amino acid concentrations.

[0009] The present invention has been made in view of the foregoing problem, and an object of the present

invention is to provide an evaluating method, a calculating method, an evaluating apparatus, a calculating apparatus, an evaluating program product, a calculating program product, a recording medium, an evaluating system, and a terminal apparatus, which can provide reliable information that may be helpful in identifying future risk of developing cerebral and cardiovascular events.

MEANS FOR SOLVING PROBLEM

[0010] To solve the problem and achieve the object, an evaluating method according to one aspect of the present disclosure includes an evaluation step of evaluating future risk of developing cerebral and cardiovascular events for a subject to be evaluated, using (i) concentration values of at least two amino acids of Gly, Cit, Trp, Met, Val, His, Pro, and Tyr in blood of the subject, or (ii) a value of a formula calculated using the concentration values and the formula including explanatory variables to be substituted with the concentration values.

[0011] In the present description, cerebral and cardiovascular events include aortic dissection, coronary diseases (myocardial infarction, heart failure, administration of percutaneous coronary intervention (PCI), and the like), and cerebrovascular disorders (stroke (cerebral infarction, intracerebral hemorrhage, subarachnoid hemorrhage), and the like).

[0012] In the present description, various amino acids are mainly written in abbreviations, the formal names of these are as follows.

| (Abbreviation) | (Formal name) |
|---|---|
| Ala | Alanine |
| Arg | Arginine |
| Asn | Asparagine |
| Cit | Citrulline |

| | |
|---|---|
| Gln | Glutamine |
| Gly | Glycine |
| His | Histidine |
| Ile | Isoleucine |
| Leu | Leucine |
| Lys | Lysine |
| Met | Methionine |
| Orn | Ornithine |
| Phe | Phenylalanine |
| Pro | Proline |
| Ser | Serine |
| Thr | Threonine |
| Trp | Tryptophan |
| Tyr | Tyrosine |
| Val | Valine |

[0013] In the evaluating method according to another aspect of the present disclosure, the at least two amino acids include Gly.

[0014] In the evaluating method according to still another aspect of the present disclosure, the at least two amino acids include any one or both of Cit and Trp.

[0015] In the evaluating method according to still another aspect of the present disclosure, the at least two amino acids include any one or both of Met and Val.

[0016] In the evaluating method according to still another aspect of the present disclosure, the evaluating step is executed by a control unit of an information processing apparatus.

[0017] A calculating method according to one aspect of the present disclosure includes a calculating step of using (i) concentration values of at least two amino acids of Gly, Cit, Trp, Met, Val, His, Pro, and Tyr in blood of a subject to be evaluated, and (ii) a formula for evaluating future

risk of developing cerebral and cardiovascular events, including explanatory variables to be substituted with the concentration values, to calculate a value of the formula.

[0018] In the calculating method according to another aspect of the present disclosure, the at least two amino acids include Gly.

[0019] In the calculating method according to still another aspect of the present disclosure, the at least two amino acids include any one or both of Cit and Trp.

[0020] In the calculating method according to still another aspect of the present disclosure, the at least two amino acids include any one or both of Met and Val.

[0021] In the calculating method according to still another aspect of the present disclosure, the evaluating step is executed by a control unit of an information processing apparatus.

[0022] An evaluating apparatus according to one aspect of the present disclosure is an evaluating apparatus including a control unit. The control unit includes an evaluating unit that evaluates future risk of developing cerebral and cardiovascular events for a subject to be evaluated, using (i) concentration values of at least two amino acids of Gly, Cit, Trp, Met, Val, His, Pro, and Tyr in blood of the subject, or (ii) a value of a formula calculated using the concentration values and the formula including explanatory variables to be substituted with the concentration values.

[0023] The evaluating apparatus according to another aspect of the present disclosure is communicatively connected via a network to a terminal apparatus that provides concentration data on the concentration values, or the value of the formula. The control unit further includes: a data-receiving unit that receives the

concentration data or the value of the formula transmitted from the terminal apparatus; and a result-sending unit that transmits an evaluation result obtained by the evaluating unit to the terminal apparatus. The evaluating unit uses the concentration values included in the concentration data or the value of the formula received by the data-receiving unit.

[0024] A calculating apparatus according to one aspect of the present disclosure is a calculating apparatus including a control unit. The control unit includes a calculating unit that uses (i) concentration values of at least two amino acids of Gly, Cit, Trp, Met, Val, His, Pro, and Tyr in blood of a subject to be evaluated, and (ii) a formula for evaluating future risk of developing cerebral and cardiovascular events, including explanatory variables to be substituted with the concentration values, to calculate a value of the formula.

[0025] An evaluating program according to one aspect of the present disclosure is an evaluating program for causing a control unit of an information processing apparatus to execute: an evaluating step of evaluating future risk of developing cerebral and cardiovascular events for a subject to be evaluated, using (i) concentration values of at least two amino acids of Gly, Cit, Trp, Met, Val, His, Pro, and Tyr in blood of the subject, or (ii) a value of a formula calculated using the concentration values and the formula including explanatory variables to be substituted with the concentration values.

[0026] A calculating program according to one aspect of the present disclosure is a calculating program for causing a control unit of an information processing apparatus to execute: a calculating step of using (i) concentration values of at least two amino acids of Gly, Cit, Trp, Met,

Val, His, Pro, and Tyr in blood of a subject to be evaluated, and (ii) a formula for evaluating future risk of developing cerebral and cardiovascular events, including explanatory variables to be substituted with the concentration values, to calculate a value of the formula.

[0027] A recording medium according to one aspect of the present disclosure is a computer readable recording medium storing the evaluating program or the calculating program. Specifically, the recording medium according to one aspect of the present disclosure is a non-transitory computer readable recording medium including programmed instructions for causing an information processing apparatus to execute the evaluating method or the calculating method.

[0028] An evaluating system according to one aspect of the present disclosure is an evaluating system including: an evaluating apparatus including a control unit; and a terminal apparatus including a control unit. The evaluating apparatus and the terminal apparatus are communicatively connected to each other via a network. The control unit of the terminal apparatus includes: a data-sending unit that transmits (i) concentration data on concentration values of at least two amino acids of Gly, Cit, Trp, Met, Val, His, Pro, and Tyr in blood of a subject to be evaluated, or (ii) a value of a formula calculated using the concentration values and the formula including explanatory variables to be substituted with the concentration values, to the evaluating apparatus; and a result-receiving unit that receives an evaluation result on future risk of developing cerebral and cardiovascular events, transmitted from the evaluating apparatus. The control unit of the evaluating apparatus includes: a data-receiving unit that receives the concentration data or the value of the formula transmitted from the terminal

apparatus; an evaluating unit that evaluates future risk of developing cerebral and cardiovascular events for the subject, using the concentration values included in the concentration data or the value of the formula received by the data-receiving unit; and a result-sending unit that transmits the evaluation result obtained by the evaluating unit to the terminal apparatus.

[0029] A terminal apparatus according to one aspect of the present disclosure is a terminal apparatus including a control unit. The control unit includes a result-obtaining unit that obtains an evaluation result on future risk of developing cerebral and cardiovascular events. The evaluation result is a result of evaluating future risk of developing cerebral and cardiovascular events for a subject to be evaluated, using (i) concentration values of at least two amino acids of Gly, Cit, Trp, Met, Val, His, Pro, and Tyr in blood of the subject, or (ii) a value of a formula calculated using the concentration values and the formula including explanatory variables to be substituted with the concentration values.

[0030] The terminal apparatus according to another aspect of the present disclosure is communicatively connected via a network to an evaluating apparatus that evaluates future risk of developing cerebral and cardiovascular events. The control unit includes a data-sending unit that transmits concentration data on the concentration values, or the value of the formula, to the evaluating apparatus. The result-obtaining unit receives the evaluation result transmitted from the evaluating apparatus.

## EFFECT OF THE INVENTION

[0031] According to the present invention, reliable

information that may be helpful in identifying future risk of developing cerebral and cardiovascular events can be provided.

## BRIEF DESCRIPTION OF DRAWINGS

[0032] FIG. 1 is a principle configurational diagram showing a basic principle of a first embodiment;

FIG. 2 is a principle configurational diagram showing a basic principle of a second embodiment;

FIG. 3 is a diagram showing an example of an entire configuration of a present system;

FIG. 4 is a diagram showing another example of an entire configuration of the present system;

FIG. 5 is a block diagram showing an example of a configuration of an evaluating apparatus 100 in the present system;

FIG. 6 is a chart showing an example of information stored in a concentration data file 106a;

FIG. 7 is a chart showing an example of information stored in an index state information file 106b;

FIG. 8 is a chart showing an example of information stored in a designated index state information file 106c;

FIG. 9 is a chart showing an example of information stored in a formula file 106d1;

FIG. 10 is a chart showing an example of information stored in an evaluation result file 106e;

FIG. 11 is a block diagram showing a configuration of an evaluating part 102d;

FIG. 12 is a block diagram showing an example of a configuration of a client apparatus 200 in the present system;

FIG. 13 is a block diagram showing an example of a configuration of a database apparatus 400 in the present

system;

FIG. 14 is a diagram of values of HR/SD and C-index;

FIG. 15 is a diagram of combinations of amino acids and values of HR/SD and C-index;

FIG. 16 is a diagram of combinations of amino acids and values of HR/SD and C-index;

FIG. 17 is a diagram of combinations of amino acids and values of HR/SD and C-index;

FIG. 18 is a diagram of values of HR/SD and C-index;

FIG. 19 is a diagram of combinations of amino acids and values of HR/SD and C-index;

FIG. 20 is a diagram of combinations of amino acids and values of HR/SD and C-index;

FIG. 21 is a diagram of combinations of amino acids and values of HR/SD and C-index;

FIG. 22 is a diagram of combinations of amino acids and values of HR/SD and C-index;

FIG. 23 is a diagram of combinations of amino acids and values of HR/SD and C-index;

FIG. 24 is a diagram of combinations of amino acids and values of HR/SD and C-index;

FIG. 25 is a diagram of combinations of amino acids and values of HR/SD and C-index;

FIG. 26 is a diagram of combinations of amino acids and values of HR/SD and C-index;

FIG. 27 is a diagram of combinations of amino acids and values of HR/SD and C-index;

FIG. 28 is a diagram of combinations of amino acids and values of HR/SD and C-index;

FIG. 29 is a diagram of combinations of amino acids and values of HR/SD and C-index;

FIG. 30 is a diagram of combinations of amino acids and values of HR/SD and C-index;

FIG. 31 is a diagram of combinations of amino acids and values of HR/SD and C-index;

FIG. 32 is a diagram of combinations of amino acids and values of HR/SD and C-index;

FIG. 33 is a diagram of combinations of amino acids and values of HR/SD and C-index;

FIG. 34 is a diagram of relative risks as to occurrence of events;

FIG. 35 is a diagram of relative risks as to occurrence of events;

FIG. 36 is a diagram of relative risks as to occurrence of events;

FIG. 37 is a diagram of relative risks as to occurrence of events;

FIG. 38 is a diagram of relative risks as to occurrence of events;

FIG. 39 is a diagram of relative risks as to occurrence of events;

FIG. 40 is a diagram of relative risks as to occurrence of events;

FIG. 41 is a diagram of relative risks as to occurrence of events;

FIG. 42 is a diagram of relative risks as to occurrence of events; and

FIG. 43 is a diagram of relative risks as to occurrence of events.

## BEST MODE(S) FOR CARRYING OUT THE INVENTION

[0033] Hereinafter, an embodiment (first embodiment) of the evaluating method and the calculating method according to the present invention and an embodiment (second embodiment) of the evaluating apparatus, the calculating apparatus, the evaluating method, the calculating method,

the evaluating program, the calculating program, the recording medium, the evaluating system, and the terminal apparatus according to the present invention are described in detail with reference to the drawings. The present invention is not limited to these embodiments.

[0034] First Embodiment

1-1. Outline of first embodiment

Here, an outline of the first embodiment will be described with reference to FIG. 1. FIG. 1 is a principle configurational diagram showing a basic principle of the first embodiment.

[0035] First, concentration data including concentration values of at least two amino acids of Gly, Cit, Trp, Met, Val, His, Pro, and Tyr in the blood (including, for example, plasma or serum) extracted from a subject to be evaluated (for example, an individual such as animal or human) is obtained (Step S11).

[0036] At Step S11, for example, the concentration data measured by a clinical laboratory or the like that measures concentrations may be obtained. For example, the following measuring method of (A), (B), or (C) may be used to measure the concentrations from the blood extracted from the subject to obtain the concentration data. In the present description, the unit of the concentration may be, for example, molar concentration, weight concentration, enzyme activity, or one obtained by addition, subtraction, multiplication, and division of any constant with these concentrations.

(A) Plasma is separated from blood by centrifuging the collected blood sample. All plasma samples are frozen and stored at -80°C until the concentration is measured. At the time of measuring the concentration, after acetonitrile is added to deproteinize the plasma samples, impurities

such as phospholipid are removed by solid phase extraction as needed, pre-column derivatization is then performed using a labeling reagent (3-aminopyridyl-N-hydroxysuccinimidyl carbamate), and the concentration is analyzed by liquid chromatograph mass spectrometry (including tandem mass spectrometry) (see International Publication WO 2003/069328 and International Publication WO 2005/116629).

(B) Plasma is separated from blood by centrifuging the collected blood sample. All plasma samples are frozen and stored at -80°C until the concentration is measured. At the time of measuring the concentration, sulfosalicylic acid is added to deproteinize the plasma samples, and the concentration is analyzed by an amino acid analyzer based on post-column derivatization using a ninhydrin reagent.

(C) Blood cell separation is performed on the collected blood sample by using a membrane, micro-electro-mechanical System (MEMS) technology, or the principle of centrifugation, whereby plasma or serum is separated from the blood. A plasma or serum sample the concentration of which is not measured immediately after obtaining the plasma or the serum is frozen and stored at -80°C until the concentration is measured. At the time of measuring the concentration, a molecule that reacts with or binds to a target substance in blood, such as an enzyme or an aptamer, is used to perform quantitative analysis and the like on an increasing or decreasing substance or a spectroscopic value by substrate recognition, whereby the concentration is analyzed.

[0037] Subsequently, future risk of developing cerebral and cardiovascular events for the subject is evaluated (predicted) using the concentration values included in the concentration data obtained at step S11 (step S12). As

used herein "future risk of developing cerebral and cardiovascular events for the subject is evaluated" includes, for example, evaluating the risk of the subject developing cerebral and cardiovascular events including stroke and myocardial infarction in the future (for example, within 10 years from blood sampling). Before step S12 is executed, data such as defectives and outliers may be removed from the concentration data obtained at step S11.

[0038] According to the first embodiment described above, the concentration data of the subject is obtained at step S11, and at step S12, the future risk of developing cerebral and cardiovascular events for the subject is evaluated using the concentration value included in the concentration data obtained at step S11 (in other words, information for evaluating future risk of developing cerebral and cardiovascular events for the subject is obtained). Thus, reliable information that may be helpful in identifying future risk of developing cerebral and cardiovascular events for the subject can be provided.

[0039] At step S12, future risk of developing cerebral and cardiovascular events for the subject may be evaluated by calculating a value of a formula using the concentration value included in the concentration data obtained at step S11 and the formula including an explanatory variable to be substituted with the concentration value.

[0040] It may be decided that the concentration value included in the concentration data reflects the future risk of developing cerebral and cardiovascular events for the subject (the same applies to the value of the formula). Furthermore, the concentration value may be converted, for example, using a method listed below, and it may be decided that the converted value reflects the future risk of developing cerebral and cardiovascular events for the

subject (the same applies to the value of the formula). In other words, the concentration value or the converted value may be treated per se as an evaluation result on the future risk of developing cerebral and cardiovascular events for the subject (the same applies to the value of the formula). The method of conversion will be described below. In the following description, the concentration value is to be converted, but the same applies to the value of the formula.

The concentration value may be converted such that a possible range of the concentration value falls within a predetermined range (for example, the range from 0.0 to 1.0, the range from 0.0 to 10.0, the range from 0.0 to 100.0, or the range from -10.0 to 10.0), for example, by addition, subtraction, multiplication, and division of any given value with the concentration value, by conversion of the concentration value by a predetermined conversion method (for example, exponential transformation, logarithm transformation, angular transformation, square root transformation, probit transformation, reciprocal transformation, Box-Cox transformation, or power transformation), or by performing a combination of these computations on the concentration value. For example, a value of an exponential function with the concentration value as an exponent and Napier constant as the base may be further calculated (specifically, a value of p/(1-p) where a natural logarithm ln(p/(1-p)) is equal to the concentration value when the probability p that the future risk of developing cerebral and cardiovascular events has a predetermined state (for example, a high risk state) is defined), and a value (specifically, a value of the probability p) may be further calculated by dividing the calculated value of the exponential function by the sum of 1 and the value of the exponential function.

The concentration value may be converted such that the converted value is a particular value when a particular condition is met. For example, the concentration value may be converted such that the converted value is 5.0 when the specificity is 40% and the converted value is 8.0 when the specificity is 95%.

For each amino acid, after normally distributing the distribution of concentration values, the concentration value may be standardized such that the mean is 50 and the standard deviation is 10. The value of the formula may be standardized such that the mean is 50 and the standard deviation is 10.

These conversions may be performed by gender or age.

[0041] The concentration value in the present description may be the concentration value itself or may be the converted value of the concentration value. The value of the formula in the present description may be the value of the formula itself or may be the converted value of the value of the formula.

[0042] Positional information about a position of a predetermined mark on a predetermined scale visually presented on a display device such as a monitor or a physical medium such as paper may be generated using the concentration value included in concentration data or, if the concentration value is converted, the converted value, and it may be decided that the generated positional information reflects the future risk of developing cerebral and cardiovascular events for the subject (the same applies to the value of the formula). The predetermined scale is for evaluating the future risk of developing cerebral and cardiovascular events and is, for example, a graduated scale at least marked with graduations corresponding to the upper limit value and the lower limit value in "a possible

range of the concentration value or the converted value", or "part of the range" (the same applies to the value of the formula). The predetermined mark corresponds to the concentration value or the converted value and is, for example, a circle sign or a star sign (the same applies to the value of the formula).

[0043] If the concentration value included in the concentration data is lower than a predetermined value (e.g., mean ±1SD, 2SD, 3SD, N quantile, N percentile, or a cutoff value the clinical significance of which is recognized) or is equal to or lower than the predetermined value, or the concentration value is equal to or higher than the predetermined value or is higher than the predetermined value, the future risk of developing cerebral and cardiovascular events for the subject may be evaluated (the same applies to the value of the formula). In this case, instead of the concentration value itself, a standard score may be used. For example, if the standard score is lower than the mean -2SD (when the standard score<30) or if the standard score is higher than the mean +2SD (when the standard score>70), the future risk of developing cerebral and cardiovascular events for the subject may be evaluated (the same applies to the value of the formula).

[0044] The future risk of developing cerebral and cardiovascular events for the subject may be evaluated qualitatively. Specifically, the subject may be classified into any one of a plurality of categories defined in consideration of at least the degree of future risk of developing cerebral and cardiovascular events, using "the concentration value included in the concentration data and preset one or more thresholds" or "the concentration value included in the concentration data, a formula including an explanatory variable to be substituted with the

concentration value, and preset one or more thresholds". The categories may include a category to which a subject with a high risk of developing belongs to, a category to which a subject with a low risk of developing belongs to, and a category to which a subject with an intermediate risk of developing belongs to. The categories may include a category to which a subject with a high risk of developing belongs to and a category to which a subject with a low risk of developing belongs to. The concentration value or the value of the formula may be converted, for example, by the method described above, and the subject may be classified into any one of the categories using the converted value.

[0045] The formula for use in evaluation is in any form and may be, for example, in the forms listed below.

- a linear model such as a multiple regression equation, a linear discriminant, principal component analysis, or canonical discriminant analysis based on the least squares method
- a generalized linear model such as logistic regression based on the maximum likelihood method
- a risk prediction model based on a semi-parametric survival analysis method by a Cox proportional hazard model or the like
- a generalized mixed linear model in consideration of random effects such as differences between individuals and differences between facilities in addition to the generalized linear model
- a formula prepared by cluster analysis such as the k-means method or hierarchical cluster analysis
- a formula prepared based on Bayesian statistics such as a Markov chain Monte Carlo (MCMC) method, a Bayesian network,

or a hierarchical Bayesian method

- a formula prepared by classification such as a support vector machine or a decision tree

- a formula prepared by a method that does not belong to the categories listed above, such as a fractional expression

- a formula represented by the sum of different forms of formulae

[0046] The formula for use in evaluation may be prepared by a method described in WO 2004/052191 that is an international application filed by the present applicant or by a method described in WO 2006/098192 that is an international application filed by the present applicant. Any formulae obtained by these methods can be preferably used in the evaluation of future risk of developing cerebral and cardiovascular events, regardless of the units of concentrations included in the concentration data as input data.

[0047] In the multiple regression equation, the multiple logistic regression equation, and the canonical discriminant function, a coefficient and a constant term are added to each explanatory variable, and the coefficient and the constant term may be preferably real numbers, more preferably values in the range of 99% confidence interval for the coefficient and the constant term obtained from data for the various kinds of classifications described above, more preferably values in the range of 95% confidence interval for the coefficient and the constant term obtained from data for the various kinds of classifications described above. The value of each coefficient and the confidence interval thereof may be those multiplied by a real number, and the value of the

constant term and the confidence interval thereof may be those having an arbitrary actual constant added or subtracted or those multiplied or divided by an arbitrary actual constant. When an expression such as the logistic regression, the linear discriminant, and the multiple regression equation is used for the evaluation, a linear transformation of the expression (addition of a constant and multiplication by a constant) and a monotonic increasing (decreasing) transformation (for example, a logit transformation) of the expression do not alter evaluation performance and thus evaluation performance after transformation is equivalent to that before transformation. Therefore, the expression includes an expression that is subjected to the linear transformation and the monotonic increasing (decreasing) transformation.

[0048] In the fractional expression, the numerator of the fractional expression is expressed by the sum of the explanatory variables A, B, C etc. and the denominator of the fractional expression is expressed by the sum of the explanatory variables a, b, c etc. The fractional expression also includes the sum of the fractional expressions $\alpha$, $\beta$, $\gamma$ etc. (for example, $\alpha+\beta$) having such constitution. The fractional expression also includes divided fractional expressions. The explanatory variables used in the numerator or denominator may have suitable coefficients respectively. The explanatory variables used in the numerator or denominator may appear repeatedly. Each fractional expression may have a suitable coefficient. A value of a coefficient for each explanatory variable and a value for a constant term may be any real numbers. In a fractional expression and the one in which explanatory variables in the numerator and explanatory variables in the denominator in the fractional expression are switched with

each other, the positive and negative signs are generally reversed in correlation with objective explanatory variables, but because their correlation is maintained, the evaluation performance can be assumed to be equivalent. The fractional expression therefore also includes the one in which explanatory variables in the numerator and explanatory variables in the denominator in the fractional expression are switched with each other.

[0049] When the future risk of developing cerebral and cardiovascular events is evaluated, a value of other biological information listed below may be used in addition to the concentration value included in the concentration data. The formula for use in evaluating future risk of developing cerebral and cardiovascular events may further include one or more explanatory variables to be substituted with a value of other biological information listed below, in addition to an explanatory variable to be substituted with the concentration value included in the concentration data. Examples of other biological information include those below.

body index measurement result (height, weight, waist circumference, BMI)

saccharometabolism index measurement result (blood glucose level, HbA1c, HOMA-IR, insulin)

liver function index measurement result (AST, ALT, γGTP)

lipid metabolism index measurement result (T-cho, LDL, HDL, TG)

nutrition-related index measurement result (total protein, albumin)

blood count index measurement result (erythrocyte, leucocyte, hematocrit, thrombocyte, lymphocyte, monocyte, neutrophil, eosinophil, basophil)

inflammation-related index measurement result (CRP)

visceral fat-related index measurement result (visceral fat area)
aortic pulse wave velocity-related index measurement result
electrocardiograph result
MRI or MRA test result
central aortic blood pressure-related index measurement result
carotid artery echo/advanced glycation end products test result
body fat measurement result
interview result on disease history (hypertension, hyperlipemia, diabetes, stroke, angina pectoris/myocardial infarction, gout, cancer, and the like)
genome information such as SNPs data and exome sequence data

[0050] Second Embodiment

2-1. Outline of the second embodiment

Here, outlines of the second embodiment will be described in detail with reference to FIG. 2. FIG. 2 is a principle configurational diagram showing a basic principle of the second embodiment. In the description of the present second embodiment, description duplicating that of the first embodiment is sometimes omitted. In particular, herein, when the future risk of developing cerebral and cardiovascular events is evaluated, a case of using the value of the formula or the converted value thereof is described as one example. However, for example, the concentration value included in the concentration data or the converted value thereof (for example, a standard score) may be used.

[0051] A control device evaluates the future risk of developing cerebral and cardiovascular events for the subject by calculating the value of the formula using (i)

the concentration values included in the previously obtained concentration data including the concentration values of at least two amino acids of Gly, Cit, Trp, Met, Val, His, Pro, and Tyr in blood of the subject (for example, an individual such as animal or human) and (ii) the formula previously stored in a memory device, including the explanatory variables to be substituted with the concentration values (step S21). Thus, reliable information that may be helpful in identifying future risk of developing cerebral and cardiovascular events can be provided.

[0052] The formula used at step S21 may be generated based on the formula-preparing processing (step 1 to step 4) described below. Here, the summary of the formula-preparing processing is described. The processing described below is merely one example, and the method of preparing the formula is not limited thereto.

[0053] First, the control device prepares a candidate formula (e.g., $y=a_1x_1+a_2x_2+...+a_nx_n$, y: index data, $x_i$: concentration data, $a_i$: constant, i=1,2,...,n) based on a predetermined formula-preparing method from index state information (data such as defective and outliers may be removed from the index state information in advance) previously stored in the memory device, containing the concentration data and index data on an index representing future risk of developing cerebral and cardiovascular events (step 1).

[0054] At step 1, a plurality of candidate formulae may be prepared from index state information using a plurality of formula preparing methods (including those for multivariate analysis, such as principal component analysis, discriminant analysis, support vector machine, multiple regression analysis, Cox regression analysis, logistic

regression analysis, k-means method, cluster analysis, and decision tree) in combination. Specifically, a plurality of groups of candidate formulae may be prepared simultaneously and concurrently using a plurality of different algorithms with index state information which is multivariate data composed of concentration data and index data obtained by analyzing blood obtained from a cerebral cardiovascular event-developing group (a group of subjects who have developed cerebral and cardiovascular events after the elapse of a certain period from blood sampling) and a cerebral cardiovascular event-free group (a group of subjects who have not developed cerebral and cardiovascular events after the elapse of a certain period from blood sampling). For example, two different candidate formulae may be prepared by performing discriminant analysis and logistic regression analysis simultaneously using different algorithms. Alternatively, the candidate formula may be prepared by converting the index state information using a candidate formula prepared by performing principal component analysis, and performing discriminant analysis of the converted index state information. In this way, a formula optimal for evaluation can be ultimately prepared.

[0055] The candidate formula prepared by the principal component analysis is a linear expression including each explanatory variable maximizing the variance of all concentration data. The candidate formula prepared by the discriminant analysis is a high-powered expression (including exponential and logarithmic expressions) including each explanatory variable minimizing the ratio of the sum of the variances in respective groups to the variance of all concentration data. The candidate formula prepared by using the support vector machine is a high-powered expression (including kernel function) including

each explanatory variable maximizing the boundary between groups. The candidate formula prepared by using the multiple regression analysis is a high-powered expression including each explanatory variable minimizing the sum of the distances from all concentration data. The candidate formula prepared by using the Cox regression analysis is a linear model including a logarithmic hazard ratio, and is a linear expression including each explanatory variable with a coefficient thereof maximizing the likelihood of the linear model. The candidate formula prepared by using the logistic regression analysis is a linear model expressing logarithmic odds of probability, and a linear expression including each explanatory variable maximizing the likelihood of the probability. The K-means method is a method of searching k pieces of neighboring concentration data in various groups, designating the group containing the greatest number of the neighboring points as its data-belonging group, and selecting the explanatory variable that makes the group to which input concentration data belong agree well with the designated group. The cluster analysis is a method of clustering (grouping) the points closest in entire concentration data. The decision tree is a method of ordering explanatory variables and predicting the group of concentration data from the pattern possibly held by the higher-ordered explanatory variable.

[0056] Returning to the description of the formula-preparing processing, the control device verifies (mutually verifies) the candidate formula prepared in step 1 based on a particular verifying method (step 2). The verification of the candidate formula is performed on each other to each candidate formula prepared in step 1. In step 2, at least one of discrimination rate, sensitivity, specificity, information criterion, ROC_AUC (area under the curve in a

receiver operating characteristic curve), and the like of the candidate formula may be verified by at least one of bootstrap method, holdout method, N-fold method, leave-one-out method, and the like. In this way, it is possible to prepare the candidate formula higher in predictability or reliability, by taking the index state information and the evaluation condition into consideration.

[0057] The discrimination rate is a rate in which a subject to be evaluated whose true state is negative is correctly evaluated as being negative by the evaluation method according to the present embodiment and a subject to be evaluated whose true state is positive is correctly evaluated as being positive by the evaluation method according to the present embodiment. The sensitivity is a rate in which a subject to be evaluated whose true state is positive is correctly evaluated as being positive by the evaluation method according to the present embodiment. The specificity is a rate in which a subject to be evaluated whose true state is negative is correctly evaluated as being negative by the evaluation method according to the present embodiment. The Akaike information criterion is a criterion representing how observation data agrees with a statistical model, for example, in the regression analysis, and it is determined that the model in which the value defined by "-2×(maximum log-likelihood of statistical model)+2×(the number of free parameters of statistical model)" is smallest is the best. ROC_AUC is defined as the area under the receiver operating characteristics curve (ROC) created by plotting (x, y)=(1-specificity, sensitivity) on two-dimensional coordinates. The value of ROC_AUC is 1 in perfect discrimination, and the closer this value is to 1, the higher the discriminative characteristic. The predictability is the average of discrimination rates,

sensitivities, or specificities obtained by repeating the validation of the candidate formula. The robustness refers to the variance of discrimination rates, sensitivities, or specificities obtained by repeating the validation of the candidate formula.

[0058] Returning to the description of the formula-preparing processing, the control device selects a combination of the concentration data contained in the index state information used in preparing the candidate formula, by selecting an explanatory variable of the candidate formula based on a predetermined explanatory variable-selecting method (step 3). In step 3, the selection of the explanatory variable may be performed on each candidate formula prepared in step 1. In this way, it is possible to select the explanatory variable of the candidate formula properly. The step 1 is executed once again by using the index state information including the concentration data selected in step 3. In step 3, the explanatory variable of the candidate formula may be selected based on at least one of stepwise method, best path method, local search method, and genetic algorithm from the verification result obtained in step 2. The best path method is a method of selecting an explanatory variable by optimizing an evaluation index of the candidate formula while eliminating the explanatory variables contained in the candidate formula one by one.

[0059] Returning to the description of the formula-preparing processing, the control device prepares the formula used for the evaluation by repeatedly performing steps 1, 2 and 3, and based on the verification results thus accumulated, selecting the candidate formula used for the evaluation from the candidate formulae (step 4). In the selection of the candidate formula, there are cases

where the optimum formula is selected from the candidate formulae prepared in the same formula-preparing method or the optimum formula is selected from all candidate formulae.

[0060] As described above, in the formula-preparing processing, the processing for the preparation of the candidate formulae, the verification of the candidate formulae, and the selection of the explanatory variables in the candidate formulae are performed based on the index state information in a series of operations in a systematized manner, whereby the formula most appropriate for evaluating future risk of developing cerebral and cardiovascular events can be prepared. In other words, in the formula-preparing processing, blood concentrations of amino acids are used in multivariate statistical analysis, and for selecting the optimum and robust combination of the explanatory variables, the explanatory variable-selecting method is combined with cross-validation to extract the formula having high evaluation performance.

[0061] 2-2. System configuration

Hereinafter, the configuration of the evaluating system according to the second embodiment (hereinafter referred to sometimes as the present system) will be described with reference to FIGS. 3 to 14. This system is merely one example, and the present invention is not limited thereto. In particular, herein, when the future risk of developing cerebral and cardiovascular events is evaluated, a case of using the value of the formula or the converted value thereof is described as one example. However, for example, the concentration value included in the concentration data or the converted value thereof (for example, a standard score) may be used.

[0062] First, an entire configuration of the present system will be described with reference to FIGS. 3 and 4.

FIG. 3 is a diagram showing an example of the entire configuration of the present system. FIG. 4 is a diagram showing another example of the entire configuration of the present system. As shown in FIG. 3, the present system is constituted in which the evaluating apparatus 100 that evaluates the future risk of developing cerebral and cardiovascular events for the individual as the subject and the client apparatus 200 (corresponding to the terminal apparatus of the present invention) that provides the concentration data of the individual, are communicatively connected to each other via a network 300.

[0063] In the present system, the client apparatus 200 that provides data for use in evaluation and the client apparatus 200 that receives the evaluation result may be different. In the present system as shown in FIG. 4, in addition to the evaluating apparatus 100 and the client apparatus 200, the database apparatus 400 storing, for example, the index state information used in preparing the formula in the evaluating apparatus 100 and the formula used for the evaluation, may be communicatively connected via the network 300.

[0064] Now, the configuration of the evaluating apparatus 100 in the present system will be described with reference to FIGS. 5 to 11. FIG. 5 is a block diagram showing an example of the configuration of the evaluating apparatus 100 in the present system, showing conceptually only the region relevant to the present invention.

[0065] The evaluating apparatus 100 includes: (i) a control device 102, such as CPU (Central Processing Unit), that integrally controls the evaluating apparatus; (ii) a communication interface 104 that connects the evaluating apparatus to the network 300 communicatively via communication apparatuses such as a router and wired or

wireless communication lines such as a private line; (iii) a memory device 106 that stores various databases, tables, files and others; and (iv) an input/output interface 108 connected to an input device 112 and an output device 114, and these parts are connected to each other communicatively via any communication channel. The evaluating apparatus 100 may be present together with various analyzers (e.g., an amino acid analyzer) in a same housing. For example, the evaluating apparatus 100 may be a compact analyzing device including components (hardware and software) that calculate (measure) concentration values of amino acids in blood and output (e.g., print or display on a monitor) the calculated value, wherein the compact analyzing device is characterized by further including the evaluating part 102d described later, and using the components to output results obtained by the evaluating part 102d.

[0066] The communication interface 104 allows communication between the evaluating apparatus 100 and the network 300 (or a communication apparatus such as a router). Thus, the communication interface 104 has a function to communicate data via a communication line with other terminals.

[0067] The input/output interface 108 is connected to the input device 112 and the output device 114. A monitor (including a home television), a speaker, or a printer may be used as the output device 114 (hereinafter, the output device 114 may be described as the monitor 114). A keyboard, a mouse, a microphone, or a monitor functioning as a pointing device together with a mouse may be used as the input device 112.

[0068] The memory device 106 is a storage means, and examples thereof include a memory apparatus such as RAM (Random Access Memory) and ROM (Read Only Memory), a fixed

disk drive such as a hard disk, a flexible disk, and an optical disk. The memory device 106 stores computer programs giving instructions to the CPU for various processings, together with OS (Operating System). As shown in the figure, the memory device 106 stores the concentration data file 106a, the index state information file 106b, the designated index state information file 106c, a formula-related information database 106d, and the evaluation result file 106e.

[0069] The concentration data file 106a stores the concentration data. FIG. 6 is a chart showing an example of information stored in the concentration data file 106a. As shown in FIG. 6, the information stored in the concentration data file 106a includes an individual number for uniquely identifying the individual (sample) as the subject and the concentration data that are correlated to one another. In FIG. 6, the concentration data is assumed to be numerical values, i.e., on a continuous scale, but the concentration data may be expressed on a nominal scale or an ordinal scale. In the case of the nominal or ordinal scale, any number may be allocated to each state for analysis. The concentration data may be combined with a value related to the other biological information (see above).

[0070] Returning to FIG. 5, the index state information file 106b stores the index state information used in preparing the formula. FIG. 7 is a chart showing an example of information stored in the index state information file 106b. As shown in FIG. 7, the information stored in the index state information file 106b includes the individual number, the index data (T) on the index representing future risk of developing cerebral and cardiovascular events (index $T_1$, index $T_2$, index $T_3$ ...),

and the concentration data that are correlated to one another. In FIG. 7, the index data and the concentration data are assumed to be numerical values, i.e., on a continuous scale, but the index data and the concentration data may be expressed on a nominal scale or an ordinal scale. In the case of the nominal or ordinal scale, any number may be allocated to each state for analysis. The index data is, for example, a known index serving as a marker of future risk of developing cerebral and cardiovascular events, and numerical data may be used.

[0071] Returning to FIG. 5, the designated index state information file 106c stores the index state information designated in a designating part 102b described below. FIG. 8 is a chart showing an example of information stored in the designated index state information file 106c. As shown in FIG. 8, the information stored in the designated index state information file 106c includes the individual number, the designated index data, and the designated concentration data that are correlated to one another.

[0072] Returning to FIG. 5, the formula-related information database 106d is composed of the formula file 106d1 storing the formula prepared in a formula-preparing part 102c described below. The formula file 106d1 stores the formulae used for the evaluation. FIG. 9 is a chart showing an example of information stored in the formula file 106d1. As shown in FIG. 9, the information stored in the formula file 106d1 includes a rank, the formula, a threshold corresponding to each formula-preparing method, and the verification result of each formula (e.g., the value of each formula) that are correlated to one another.

[0073] Returning to FIG. 5, the evaluation result file 106e stores the evaluation results obtained in the evaluating part 102d described below. FIG. 10 is a chart

showing an example of information stored in the evaluation result file 106e. The information stored in the evaluation result file 106e includes the individual number for uniquely identifying the individual (sample) as the subject, the concentration data of the individual, and the evaluation result on the future risk of developing cerebral and cardiovascular events (for example, the value of the formula calculated by a calculating part 102d1 described below, the converted value of the value of the formula obtained by a converting part 102d2 described below, the positional information generated by a generating part 102d3 described below, or the classification result obtained by a classifying part 102d4 described below), that are correlated to one another.

[0074] Returning to FIG. 5, the control device 102 has an internal memory storing, for example, control programs such as OS (Operating System), programs for various processing procedures, and other needed data, and performs various information processings according to these programs. As shown in the figure, the control device 102 includes mainly an obtaining part 102a, the designating part 102b, the formula-preparing part 102c, the evaluating part 102d, a result outputting part 102e, and a sending part 102f. The control device 102 performs data processings such as removal of data including defective, removal of data including many outliers, and removal of explanatory variables for the defective-including data in the index state information transmitted from the database apparatus 400 and in the concentration data transmitted from the client apparatus 200.

[0075] The obtaining part 102a obtains information (specifically, concentration data, index state information, formula, and the like). For example, the obtaining part

102a may receive information (specifically, concentration data, index state information, formula, and the like) transmitted from the client apparatus 200 or the database apparatus 400 via the network 300 to obtain information. The obtaining part 102a may receive data for use in evaluation transmitted from a client apparatus 200 different from the client apparatus 200 to which the evaluation result is transmitted. When the evaluating apparatus 100 includes a mechanism (including hardware and software) for reading information recorded on a recording medium, the obtaining part 102a may obtain information by reading information recorded on a recording medium (specifically, concentration data, index state information, formula, and the like) through the mechanism. The specifying part 102b specifies target index data and concentration data in creating a formula.

[0076] The formula-preparing part 102c generates the formula based on the index state information obtained in the obtaining part 102a or the index state information designated in the designating part 102b. If the formulae are stored previously in a predetermined region of the memory device 106, the formula-preparing part 102c may generate the formula by selecting the desired formula out of the memory device 106. Alternatively, the formula-preparing part 102c may generate the formula by selecting and downloading the desired formula from another computer apparatus (e.g., the database apparatus 400) in which the formulae are previously stored.

[0077] The evaluating part 102d evaluates the future risk of developing cerebral and cardiovascular events for the individual by calculating the value of the formula using the previously obtained formula (for example, the formula prepared by the formula-preparing part 102c or the

formula obtained by the obtaining part 102a) and the concentration value included in the concentration data obtained by the obtaining part 102a. The evaluating part 102d may evaluate the future risk of developing cerebral and cardiovascular events for the individual using the concentration value included in the concentration data or the converted value of the concentration value (for example, the standard score).

[0078] Hereinafter, a configuration of the evaluating part 102d will be described with reference to FIG. 11. FIG. 11 is a block diagram showing the configuration of the evaluating part 102d, and only a part in the configuration related to the present invention is shown conceptually. The evaluating part 102d includes the calculating part 102d1, the converting part 102d2, the generating part 102d3, and the classifying part 102d4, additionally.

[0079] The calculating part 102d1 uses (i) the concentration value included in the concentration data and (ii) the formula including the explanatory variable to be substituted with the concentration value, to calculate the value of the formula. The evaluating part 102d may store the value of the formula calculated by the calculating part 102d1 as the evaluation result in a predetermined region of the evaluation result file 106e.

[0080] The converting part 102d2 converts the value of the formula calculated by the calculating part 102d1, for example, by the conversion method described above. The evaluating part 102d may store the converted value by the converting part 102d2 as the evaluation result in a predetermined region of the evaluation result file 106e. The converting part 102d2 may convert the concentration value included in the concentration data, for example, by the conversion method described above.

[0081] The generating part 102d3 generates the positional information about the position of the predetermined mark on the predetermined scale visually presented on the display device such as a monitor or the physical medium such as paper, using the value of the formula calculated by the calculating part 102d1 or the converted value by the converting part 102d2 (the concentration value or the converted value of the concentration value may be used as well). The evaluating part 102d may store the positional information generated by the generating part 102d3 as the evaluation result in a predetermined region of the evaluation result file 106e.

[0082] The classifying part 102d4 classifies the individual into any one of the categories defined at least considering the degree of future risk of developing cerebral and cardiovascular events, using the value of the formula calculated by the calculating part 102d1 or the converted value by the converting part 102d2 (the concentration value or the converted value of the concentration value may be used as well).

[0083] The result outputting part 102e outputs, into the output device 114, for example, the processing results in each processing part in the control device 102 (including the evaluation results obtained by the evaluating part 102d).

[0084] The sending part 102f transmits the evaluation results to the client apparatus 200 that is a sender of the concentration data of the individual, and transmits the formulae prepared in the evaluating apparatus 100 and the evaluation results to the database apparatus 400. The sending part 102f may transmit the evaluation result to a client apparatus 200 different from the client apparatus 200 that from which data for use in evaluation is

transmitted.

[0085] Hereinafter, a configuration of the client apparatus 200 in the present system will be described with reference to FIG. 12. FIG. 12 is a block diagram showing an example of the configuration of the client apparatus 200 in the present system, and only the part in the configuration relevant to the present invention is shown conceptually.

[0086] The client apparatus 200 includes a control device 210, ROM 220, HD (Hard Disk) 230, RAM 240, an input device 250, an output device 260, an input/output IF 270, and a communication IF 280 that are connected communicatively to one another through a communication channel. The client apparatus 200 may be realized based on an information processing apparatus (for example, an information processing terminal such as a known personal computer, a workstation, a family computer, Internet TV (Television), PHS (Personal Handyphone System) terminal, a mobile phone terminal, a mobile unit communication terminal, or PDA (Personal Digital Assistants)) connected as needed with peripheral devices such as a printer, a monitor, and an image scanner.

[0087] The input device 250 is, for example, a keyboard, a mouse, or a microphone. The monitor 261 described below also functions as a pointing device together with a mouse. The output device 260 is an output means for outputting information received via the communication IF 280, and includes the monitor 261 (including home television) and a printer 262. In addition, the output device 260 may have a speaker or the like additionally. The input/output IF 270 is connected to the input device 250 and the output device 260.

[0088] The communication IF 280 connects the client

apparatus 200 to the network 300 (or communication apparatus such as a router) communicatively. In other words, the client apparatus 200 is connected to the network 300 via a communication apparatus such as a modem, TA (Terminal Adapter) or a router, and a telephone line, or via a private line. In this way, the client apparatus 200 can access to the evaluating apparatus 100 by using a particular protocol.

[0089] The control device 210 has a receiving part 211 and a sending part 212. The receiving part 211 receives various kinds of information such as the evaluation results transmitted from the evaluating apparatus 100, via the communication IF 280. The sending part 212 sends various kinds of information such as the concentration data of the individual, via the communication IF 280, to the evaluating apparatus 100.

[0090] All or a part of processings of the control device 210 may be performed by CPU and programs read and executed by the CPU. Computer programs for giving instructions to the CPU and executing various processings together with the OS (Operating System) are recorded in the ROM 220 or HD 230. The computer programs, which are executed as they are loaded in the RAM 240, constitute the control device 210 with the CPU. The computer programs may be stored in application program servers connected via any network to the client apparatus 200, and the client apparatus 200 may download all or a part of them as needed. All or any part of processings of the control device 210 may be realized by hardware such as wired-logic.

[0091] The control device 210 may include an evaluating part 210a (including a calculating part 210a1, a converting part 210a2, a generating part 210a3, and a classifying part 210a4) having the same functions as the functions of the

evaluating part 102d in the evaluating apparatus 100. When the control device 210 includes the evaluating part 210a, the evaluating part 210a may convert the value of the formula (the concentration value may be used as well) in the converting part 210a2, generate the positional information corresponding to the value of the formula or the converted value (the concentration value or the converted value of the concentration value may be used as well) in the generating part 210a3, and classify the individual into any one of the categories using the value of the formula or the converted value (the concentration value or the converted value of the concentration value may be used as well) in the classifying part 210a4, in accordance with information included in the evaluation results transmitted from the evaluating apparatus 100.

[0092] Hereinafter, the network 300 in the present system will be described with reference to FIGS. 3 and 4. The network 300 has a function to connect the evaluating apparatus 100, the client apparatuses 200, and the database apparatus 400 mutually, communicatively to one another, and is for example the Internet, an intranet, or LAN (Local Area Network (including both wired and wireless)). The network 300 may be VAN (Value Added Network), a personal computer communication network, a public telephone network (including both analog and digital), a leased line network (including both analog and digital), CATV (Community Antenna Television) network, a portable switched network or a portable packet-switched network (including IMT2000 (International Mobile Telecommunication 2000) system, GSM (registered trademark) (Global System for Mobile Communications) system, or PDC (Personal Digital Cellular)/PDC-P system), a wireless calling network, a local wireless network such as Bluetooth (registered

trademark), PHS network, a satellite communication network (including CS (Communication Satellite), BS (Broadcasting Satellite), ISDB (Integrated Services Digital Broadcasting), and the like), or the like.

[0093] Hereinafter, the configuration of the database apparatus 400 in the present system will be described with reference to FIG. 13. FIG. 13 is a block diagram showing an example of the configuration of the database apparatus 400 in the present system, showing conceptually only the region relevant to the present invention.

[0094] The database apparatus 400 has functions to store, for example, the index state information used in preparing the formulae in the evaluating apparatus 100 or the database apparatus, the formulae prepared in the evaluating apparatus 100, and the evaluation results obtained in the evaluating apparatus 100. As shown in FIG. 13, the database apparatus 400 includes; (i) a control device 402, such as CPU, that integrally controls the database apparatus; (ii) a communication interface 404 connecting the database apparatus to the network 300 communicatively via communication apparatuses such as a router and wired or wireless communication circuits such as a private line; (iii) a memory device 406 storing various databases, tables, files (for example, files for Web pages) and others; and (iv) an input/output interface 408 connected to an input device 412 and an output device 414, and these parts are connected communicatively to each other via any communication channel.

[0095] The memory device 406 is a storage means, and, examples thereof include a memory apparatus such as RAM or ROM, a fixed disk drive such as a hard disk, a flexible disk, and an optical disk. The memory device 406 stores, for example, various programs used in various processings.

The communication interface 404 allows communication between the database apparatus 400 and the network 300 (or a communication apparatus such as a router). Thus, the communication interface 404 has a function to communicate data via a communication line with other terminals. The input/output interface 408 is connected to the input device 412 and the output device 414. A monitor (including a home television), a speaker, or a printer may be used as the output device 414. A keyboard, a mouse, a microphone, or a monitor functioning as a pointing device together with a mouse may be used as the input device 412.

[0096] The control device 402 has an internal memory storing, for example, control programs such as OS (Operating System), programs for various processing procedures, and other needed data, and performs various information processings according to these programs. As shown in the figure, the control device 402 includes mainly a sending part 402a and a receiving part 402b. The sending part 402a transmits various kinds of information such as the index state information and the formulae to the evaluating apparatus 100. The receiving part 402b receives various kinds of information such as the formula and the evaluation results, transmitted from the evaluating apparatus 100.

[0097] In the present description, the evaluating apparatus 100 executes the obtainment of the concentration data, the calculation of the value of the formula, the classification of the individual into the category, and the transmission of the evaluation results, while the client apparatus 200 executes the reception of the evaluation results, described as an example. However, when the client apparatus 200 includes the evaluating unit 210a, the evaluating apparatus 100 only has to execute the

calculation of the value of the formula. For example, the conversion of the value of the formula, the generation of the positional information, and the classification of the individual into the category may be appropriately shared between the evaluating apparatus 100 and the client apparatus 200.

For example, when the client apparatus 200 receives the value of the formula from the evaluating apparatus 100, the evaluating unit 210a may convert the value of the formula in the converting unit 210a2, generate the positional information corresponding to the value of the formula or the converted value in the generating unit 210a3, and classify the individual into any one of the categories using the value of the formula or the converted value in the classifying unit 210a4.

When the client apparatus 200 receives the converted value from the evaluating apparatus 100, the evaluating unit 210a may generate the positional information corresponding to the converted value in the generating unit 210a3, and classify the individual into any one of the categories using the converted value in the classifying unit 210a4.

When the client apparatus 200 receives the value of the formula or the converted value and the positional information from the evaluating apparatus 100, the evaluating unit 210a may classify the individual into any one of the categories using the value of the formula or the converted value in the classifying unit 210a4.

[0098] 2-3. Other embodiments

In addition to the second embodiment described above, the evaluating apparatus, the calculating apparatus, the evaluating method, the calculating method, the evaluating program, the calculating program, the recording medium, the

evaluating system, and the terminal apparatus according to the present invention can be practiced in various different embodiments within the technological scope of the claims.

[0099] Of the processings described in the second embodiment, all or a part of the processings described as automatically performed ones may be manually performed, or all or a part of the processings described as manually performed ones may be also automatically performed by known methods.

[0100] In addition, the processing procedures, the control procedures, the specific names, the information including parameters such as registered data of various processings and retrieval conditions, the screen examples, and the database configuration shown in the description and the drawings may be arbitrarily modified unless otherwise specified.

[0101] The components of the evaluating apparatus 100 shown in the figures are functionally conceptual and therefore not be physically configured as shown in the figures.

[0102] For example, for the operational functions provided in the evaluating apparatus 100, in particular, for the operational functions performed in the control device 102, all or part thereof may be implemented by the CPU (Central Processing Unit) and programs interpreted and executed in the CPU, or may be implemented by wired-logic hardware. The program is recorded in a non-transitory tangible computer-readable recording medium including programmed instructions for making an information processing apparatus execute the evaluating method or the calculating method according to the present invention, and is mechanically read as needed by the evaluating apparatus 100. More specifically, computer programs to give

instructions to the CPU in cooperation with the OS (operating system) to perform various processes are recorded in the memory device 106 such as ROM or a HDD (hard disk drive). The computer programs are executed by being loaded to RAM, and form the control unit in cooperation with the CPU.

[0103] The computer programs may be stored in an application program server connected to the evaluating apparatus 100 via an arbitrary network, and all or part thereof can be downloaded as necessary.

[0104] The evaluating program or the calculating program according to the present invention may be stored in the non-transitory tangible computer-readable recording medium, or can be configured as a program product. The "recording medium" mentioned here includes any "portable physical medium" such as a memory card, a USB (universal serial bus) memory, an SD (secure digital) card, a flexible disk, a magneto-optical disc, ROM, EPROM (erasable programmable read only memory), EEPROM (registered trademark) (electronically erasable and programmable read only memory), CD-ROM (compact disk read only memory), MO (magneto-optical disk), DVD (digital versatile disk), and Blu-ray (registered trademark) Disc.

[0105] The "program" mentioned here is a data processing method described in an arbitrary language or description method, and therefore any form such as a source code and a binary code is acceptable. The "program" is not necessarily limited to a program configured as a single unit, and, therefore, includes those dispersively configured as a plurality of modules and libraries and those in which the function of the program is achieved in cooperation with separate programs represented as OS (operating system). Any known configuration and procedures

can be used as a specific configuration and reading procedure to read a recording medium by each apparatus shown in the embodiments, an installation procedure after the reading, and the like.

[0106] The various databases and the like stored in the memory device 106 is a storage unit such as a memory device such as RAM and ROM, a fixed disk drive such as a hard disk, a flexible disk, or an optical disc. The memory device 106 stores therein various programs, tables, databases, files for Web (World Wide Web) pages, and the like used to perform various processes and to provide Web sites.

[0107] The evaluating apparatus 100 may be configured as an information processing apparatus such as known personal computer and work station, or may be configured as the information processing apparatus connected to an arbitrary peripheral device. The evaluating apparatus 100 may be provided by installing software (including the programs and the data, etc.) to cause the information processing apparatus to implement the evaluating method or the calculating method according to the present invention.

[0108] Furthermore, a specific configuration of dispersion or integration of the apparatuses is not limited to the shown one. The apparatuses can be configured by functionally or physically dispersing or integrating all or part of the apparatuses in arbitrary units according to various types of additions or the like or according to functional loads. In other words, the embodiments may be implemented in arbitrary combinations thereof or an embodiment may be selectively implemented.

Example 1

[0109] Medical checkups were conducted for residents from 2008 to 2010, and blood sampled in the checkups was measured by the amino acid analyzing method (A) to

determine the free amino acid concentration in blood. For the group of residents, follow-up study was conducted for up to 10 years from the timing of the medical checkups to 2018 as to whether cerebral and cardiovascular events (stroke (cerebral infarction, intracerebral hemorrhage, subarachnoid hemorrhage), myocardial infarction, or PCI administration) occurred. In this group, 4039 residents who had blood taken in the morning and underwent a medical checkup more than 8 hours after meal ingestion were targeted. Among them, event incident cases were 64 people out of 4039 people, 32 cases developed stroke, 22 cases developed myocardial infarction, and 10 cases had PCI administered.

[0110] A value of a linear predictor was obtained by substituting the measured free amino acid concentration in blood into the formulae (three formulae below) for discriminating whether cardiovascular events occur according to the description in the Patent Document 1 (JP-A-2013-178238). The hazard ratio per standard deviation (HR/SD) and C-index of the obtained value of the linear predictor on the occurrence of cerebral and cardiovascular events were calculated. The calculation results are listed in FIG. 14. C-index is an index proposed by Harrell et al. to represent the accuracy of prognostic prediction and is a nonparametric index representing a matching degree of the magnitude relation of the event probabilities predicted from a model and the magnitude relation of the actual event probabilities.

logistic regression: 0.3452-0.009171*Ser-0.01119*Thr+0.006555*Lys+0.01067*Arg-0.03345*Trp

linear regression: -0.5164+0.0018*Pro-0.004*Thr+0.0038*Orn+0.0026*Arg-0.0074*Trp

Cox proportional hazard model: 0.0042*Pro-

0.0133*Thr+0.0075*Lys+0.0137*Cit-0.0279*Trp

[0111] All combinations of two amino acids selected from 19 kinds of amino acids (Thr, Ser, Asn, Gln, Pro, Gly, Ala, Cit, Val, Met, Ile, Leu, Tyr, Phe, His, Trp, Orn, Lys, and Arg) were extracted, and the measured free amino acid concentration in blood was substituted into the Cox proportional hazard model corresponding to each of the extracted combinations to obtain the value of the linear predictor of the model. HR/SD and C-index of the obtained value of the linear predictor on whether cerebral and cardiovascular events occur in the follow-up period were calculated. Combinations of two amino acids exhibiting a higher value of HR/SD or C-index than the values listed in FIG. 14 are listed in FIG. 15 to FIG. 17. FIG. 15 to FIG. 17 depict combinations of two amino acids in the Cox proportional hazard model including two amino acids in which the value of HR/SD or C-index is higher than the values listed in FIG. 14, and the values of HR/SD and C-index.

Example 2

[0112] In the group described in Example 1, 5479 residents who had blood taken in the morning or in the afternoon and underwent a medical checkup more than 8 hours after meal ingestion in 2008 or 2009 were targeted. Among them, event incident cases were 104 people out of 5479 people, 50 cases developed stroke, 35 cases developed myocardial infarction, and 19 cases had PCI administered.

[0113] The measured free amino acid concentration in blood was substituted into three formulae described in Patent Document 1 described in Example 1. HR/SD and C-index of the obtained value of the linear predictor on the occurrence of cerebral and cardiovascular events were calculated. The calculation results are listed in FIG. 18.

[0114] All combinations of two amino acids selected from the 19 kinds of amino acids were extracted, and the measured free amino acid concentration in blood was substituted into the Cox proportional hazard model corresponding to each of the combinations to obtain the value of the linear predictor of the model. HR/SD and C-index of the obtained value of the linear predictor on whether cerebral and cardiovascular events occur in the follow-up period were calculated. Combinations of two amino acids exhibiting a higher value of HR/SD or C-index than the values listed in FIG. 18 are listed in FIG. 19 to FIG. 20. FIG. 19 and FIG. 20 depict combinations of two amino acids in the Cox proportional hazard model including two amino acids in which the value of HR/SD or C-index is higher than the values listed in FIG. 18, and the values of HR/SD and C-index.

Example 3

[0115] The targets were 4039 residents described in Example 1.

[0116] All combinations of two amino acids selected from 13 kinds of amino acids (Gly, Gln, His, Thr, Cit, Pro, Tyr, Val, Met, Lys, Ile, Phe, and Trp) were extracted, and the measured free amino acid concentration in blood was substituted into the Cox proportional hazard model corresponding to each of the extracted combinations to obtain the value of the linear predictor of the model. HR/SD and C-index of the obtained value of the linear predictor on whether cerebral and cardiovascular events occur in the follow-up period were calculated. Combinations of two amino acids exhibiting a higher value of HR/SD or C-index than the values listed in FIG. 14 are listed in FIG. 21 to FIG. 22. FIG. 21 and FIG. 22 depict combinations of two amino acids in the Cox proportional

hazard model including two amino acids in which HR/SD or C-index is higher than the values listed in FIG. 14, and the values of HR/SD and C-index.

Example 4

[0117] The targets were 5479 residents described in Example 2.

[0118] All combinations of two amino acids selected from the 13 kinds of amino acids were extracted, and the measured free amino acid concentration in blood was substituted in the Cox proportional hazard model corresponding to each of the extracted combinations to obtain the value of the linear predictor of the model. HR/SD and C-index of the obtained value of the linear predictor on whether cerebral and cardiovascular events occur in the follow-up period were calculated. Combinations of two amino acids exhibiting a higher value of HR/SD or C-index than the values listed in FIG. 18 are listed in FIG. 23. FIG. 23 depicts combinations of two amino acids in the Cox proportional hazard model including two amino acids in which HR/SD or C-index is higher than the values listed in FIG. 18, and the values of HR/SD and C-index.

Example 5

[0119] The targets were 4039 residents described in Example 1.

[0120] All combinations of three amino acids selected from the 19 kinds of amino acids were extracted, and the measured free amino acid concentration in blood was substituted into the Cox proportional hazard model corresponding to each of the extracted combinations to obtain the value of the linear predictor of the model. HR/SD and C-index of the obtained value of the linear predictor on whether cerebral and cardiovascular events

occur in the follow-up period were calculated. Combinations of three amino acids exhibiting a higher value of HR/SD or C-index than the values listed in FIG. 21 and FIG. 22 are listed in FIG. 24. FIG. 24 depicts combinations of three amino acids in the Cox proportional hazard model including three amino acids in which HR/SD or C-index is higher than the values listed in FIG. 21 and FIG. 22, and the values of HR/SD and C-index.

Example 6

[0121] The targets were 5479 residents described in Example 2.

[0122] All combinations of three amino acids selected from the 19 kinds of amino acids were extracted, and the measured free amino acid concentration in blood was substituted into the Cox proportional hazard model corresponding to each of the extracted combinations to obtain the value of the linear predictor of the model. HR/SD and C-index of the obtained value of the linear predictor on whether cerebral and cardiovascular events occur in the follow-up period were calculated. Combinations of three amino acids exhibiting a higher value of HR/SD or C-index than the values listed in FIG. 23 are listed in FIG. 25. FIG. 25 depicts combinations of three amino acids in the Cox proportional hazard model including three amino acids in which HR/SD or C-index is higher than the values listed in FIG. 23, and the values of HR/SD and C-index.

Example 7

[0123] The targets were 4039 residents described in Example 1.

[0124] All combinations of three amino acids selected from the 13 kinds of amino acids were extracted, and the measured free amino acid concentration in blood was

substituted into the Cox proportional hazard model corresponding to each of the extracted combinations to obtain the value of the linear predictor of the model. HR/SD and C-index of the obtained value of the linear predictor on whether cerebral and cardiovascular events occur in the follow-up period were calculated. Combinations of three amino acids exhibiting a higher value of HR/SD or C-index than the values listed in FIG. 24 are listed in FIG. 26. FIG. 26 depicts combinations of three amino acids in the Cox proportional hazard model including three amino acids in which HR/SD or C-index is higher than the values listed in FIG. 24, and the values of HR/SD and C-index.

Example 8

[0125] The targets were 5479 residents described in Example 2.

[0126] All combinations of three amino acids selected from the 13 kinds of amino acids were extracted, and the measured free amino acid concentration in blood was substituted into the Cox proportional hazard model corresponding to each of the extracted combinations to obtain the value of the linear predictor of the model. HR/SD and C-index of the obtained value of the linear predictor on whether cerebral and cardiovascular events occur in the follow-up period were calculated. Combinations of three amino acids exhibiting a higher value of HR/SD or C-index than the values listed in FIG. 25 are listed in FIG. 27. FIG. 27 depicts combinations of three amino acids in the Cox proportional hazard model including three amino acids in which HR/SD or C-index higher than the values listed in FIG. 25, and the values of HR/SD and C-index.

Example 9

[0127] The targets were 4039 residents described in Example 1.

[0128] All combinations of four or more and six or less amino acids selected from the 13 kinds of amino acids were extracted, and the measured free amino acid concentration in blood was substituted into the Cox proportional hazard model corresponding to each of the extracted combinations to obtain the value of the linear predictor of the model. HR/SD and C-index of the obtained value of the linear predictor on whether cerebral and cardiovascular events occur in the follow-up period were calculated. Combinations of four or more and six or less amino acids exhibiting a higher value of HR/SD or C-index than the values listed in FIG. 26 are listed in FIG. 28. FIG. 28 depicts combinations of four or more and six or less amino acids in the Cox proportional hazard model including four or more and six or less amino acids in which HR/SD or C-index is higher than the values listed in FIG. 26, and the values of HR/SD and C-index.

Example 10

[0129] The targets were 5479 residents described in Example 2.

[0130] All combinations of four or more and six or less amino acids selected from the 13 kinds of amino acids were extracted, and the measured free amino acid concentration in blood was substituted into the Cox proportional hazard model corresponding to each of the extracted combinations to obtain the value of the linear predictor of the model. HR/SD and C-index of the obtained value of the linear predictor on whether cerebral and cardiovascular events occur in the follow-up period were calculated. Combinations of four or more and six or less amino acids exhibiting a higher value of HR/SD or C-index than the

values listed in FIG. 27 are listed in FIG. 29 to FIG. 33. FIG. 29 to FIG. 33 depict combinations of four or more and six or less amino acids in the Cox proportional hazard model including four or more and six or less amino acids in which HR/SD or C-index is higher than the values listed in FIG. 27, and HR/SD and C-index.

Example 11

[0131] The targets were 4039 residents described in Example 1.

[0132] The 40% point and the 95% point of the value of the linear predictor of the model described in Example 9 were set as cut-off values, and rank classification of the subjects was conducted. Specifically, the subject with a value of the linear predictor less than the 40% point was classified as rank A, the subject with a value equal to or more than the 40% point and less than the 95% point was classified as rank B, and the subject with a value equal to or more than the 95% point was classified as rank C.

[0133] For each combination of four or more and six or less amino acids, a relative risk of subjects who fall into rank B to subjects who fall into rank A, and a relative risk of subjects who fall into rank C to subjects who fall into rank A as to whether cerebral and cardiovascular events occur during the follow-up period were calculated.

[0134] For each combination of four or more and six or less amino acids, a relative risk of subjects who fall into rank B to subjects who fall into rank A and a relative risk of subjects who fall into rank C to subject who fall into rank A as to whether cerebrovascular events occur during the follow-up period were calculated.

[0135] For each combination of four or more and six or less amino acids, a relative risk of subjects who fall into rank B to subjects who fall into rank A and a relative risk

of subjects who fall into rank C to subjects who fall into rank A as to whether cardiovascular events occur during the follow-up period were calculated.

[0136] The calculated relative risks are listed in FIG. 34. FIG. 34 depicts a relative risk as to the occurrence of cerebral and cardiovascular events, a relative risk as to the occurrence of cerebrovascular events, and a relative risk as to the occurrence of cardiovascular events of subjects who fall into rank B to subjects who fall into rank A and of subjects who fall into rank C to subjects who fall into rank A when rank classification of the subjects was conducted based on the value of the linear predictor of the Cox proportional hazard model described in Example 9.

Example 12

[0137] The targets were 5479 residents described in Example 2.

[0138] The 40% point and the 95% point of the value of the linear predictor of the model described in Example 10 were set as cut-off values, and rank classification of the subjects was conducted. Specifically, the subject with a value of the linear predictor less than the 40% point was classified as rank A, the subject with a value equal to or more than the 40% point and less than the 95% point was classified as rank B, and the subject with a value equal to or more than the 95% point was classified as rank C.

[0139] For each combination of four or more and six or less amino acids, a relative risk of subjects who fall into rank B to subjects who fall into rank A and a relative risk of subjects who fall into rank C to subjects who fall into rank A as to whether cerebral and cardiovascular events occur during the follow-up period were calculated.

[0140] For each combination of four or more and six or less amino acids, a relative risk of subjects who fall into

rank B to subjects who fall into rank A and a relative risk of subjects who fall into rank C to subjects who fall into rank A as to whether cerebrovascular events occur during the follow-up period were calculated.

[0141] For each combination of four or more and six or less amino acids, a relative risk of subjects who fall into rank B to subjects who fall into rank A and a relative risk of subjects who fall into rank C to subjects who fall into rank A as to whether cardiovascular events occur during the follow-up period were calculated.

[0142] The calculated relative risks are listed in FIG. 35 to FIG. 43. FIG. 35 to FIG. 43 depict a relative risk as to the occurrence of cerebral and cardiovascular events, a relative risk as to the occurrence of cerebrovascular events, and a relative risk as to the occurrence of cardiovascular events of subjects who fall into rank B to subjects who fall into rank A and of subjects who fall into rank C to subjects who fall into rank A when rank classification of the subjects was conducted based on the value of the linear predictor of the Cox proportional hazard model described in Example 10.

INDUSTRIAL APPLICABILITY

[0143] As described above, the present invention may be practiced widely in many industrial fields, in particular in pharmaceutical, food, and medical fields, and is extremely useful in the field of bioinformatics, for example, performing prediction of future risk of developing cerebral and cardiovascular events.

EXPLANATION OF LETTERS OR NUMERALS

[0144] 100 Evaluating apparatus

102 Control device

102a Obtaining part

102b Designating part

102c Formula-preparing part

102d Evaluating part

102d1 Calculating part

102d2 Converting part

102d3 Generating part

102d4 Classifying part

102e Result outputting part

102f Sending part

104 Communication interface

106 Memory device

106a Concentration data file

106b Index state information file

106c Designated index state information file

106d Formula-related information database

106d1 Formula file

106e Evaluation result file

108 Input/output interface

112 Input device

114 Output device

200 Client apparatus (terminal apparatus (information communication terminal apparatus))

300 Network

400 Database apparatus

CLAIMS

1. An evaluating method comprising:

an evaluation step of evaluating future risk of developing cerebral and cardiovascular events for a subject to be evaluated, using (i) concentration values of at least two amino acids of Gly, Cit, Trp, Met, Val, His, Pro, and Tyr in blood of the subject, or (ii) a value of a formula calculated using the concentration values and the formula including explanatory variables to be substituted with the concentration values.

2. The evaluating method according to claim 1, wherein the at least two amino acids include Gly.

3. The evaluating method according to claim 1 or 2, wherein the at least two amino acids include any one or both of Cit and Trp.

4. The evaluating method according to any one of claims 1 to 3, wherein the at least two amino acids include any one or both of Met and Val.

5. The evaluating method according to any one of claims 1 to 4, wherein the evaluating step is executed by a control unit of an information processing apparatus.

6. A calculating method comprising:

a calculating step of using (i) concentration values of at least two amino acids of Gly, Cit, Trp, Met, Val, His, Pro, and Tyr in blood of a subject to be evaluated, and (ii) a formula for evaluating future risk of developing cerebral and cardiovascular events, including explanatory variables to be substituted with the concentration values,

to calculate a value of the formula.

7. The calculating method according to claim 6, wherein the at least two amino acids include Gly.

8. The calculating method according to claim 6 or 7, wherein the at least two amino acids include any one or both of Cit and Trp.

9. The evaluating method according to any one of claims 6 to 8, wherein the at least two amino acids include any one or both of Met and Val.

10. The evaluating method according to any one of claims 6 to 9, wherein the evaluating step is executed by a control unit of an information processing apparatus.

11. An evaluating apparatus comprising a control unit, wherein the control unit includes:

an evaluating unit that evaluates future risk of developing cerebral and cardiovascular events for a subject to be evaluated, using (i) concentration values of at least two amino acids of Gly, Cit, Trp, Met, Val, His, Pro, and Tyr in blood of the subject, or (ii) a value of a formula calculated using the concentration values and the formula including explanatory variables to be substituted with the concentration values.

12. The evaluating apparatus according to claim 11, being communicatively connected via a network to a terminal apparatus that provides concentration data on the concentration values, or the value of the formula,

wherein the control unit further includes:

a data-receiving unit that receives the concentration data or the value of the formula transmitted from the terminal apparatus; and

a result-sending unit that transmits an evaluation result obtained by the evaluating unit to the terminal apparatus,

wherein the evaluating unit uses the concentration values included in the concentration data or the value of the formula received by the data-receiving unit.

13. A calculating apparatus comprising a control unit, wherein the control unit includes:

a calculating unit that uses (i) concentration values of at least two amino acids of Gly, Cit, Trp, Met, Val, His, Pro, and Tyr in blood of a subject to be evaluated, and (ii) a formula for evaluating future risk of developing cerebral and cardiovascular events, including explanatory variables to be substituted with the concentration values, to calculate a value of the formula.

14. An evaluating program for causing a control unit of an information processing apparatus to execute:

an evaluating step of evaluating future risk of developing cerebral and cardiovascular events for a subject to be evaluated, using (i) concentration values of at least two amino acids of Gly, Cit, Trp, Met, Val, His, Pro, and Tyr in blood of the subject, or (ii) a value of a formula calculated using the concentration values and the formula including explanatory variables to be substituted with the concentration values.

15. A calculating program for causing a control unit of an information processing apparatus to execute:

a calculating step of using (i) concentration values of at least two amino acids of Gly, Cit, Trp, Met, Val, His, Pro, and Tyr in blood of a subject to be evaluated, and (ii) a formula for evaluating future risk of developing cerebral and cardiovascular events, including explanatory variables to be substituted with the concentration values, to calculate a value of the formula.

16. A computer readable recording medium storing the evaluating program according to claim 14 or the calculating program according to claim 15.

17. An evaluating system comprising:

an evaluating apparatus including a control unit; and

a terminal apparatus including a control unit,

wherein the evaluating apparatus and the terminal apparatus are communicatively connected to each other via a network,

the control unit of the terminal apparatus includes:

a data-sending unit that transmits (i) concentration data on concentration values of at least two amino acids of Gly, Cit, Trp, Met, Val, His, Pro, and Tyr in blood of a subject to be evaluated, or (ii) a value of a formula calculated using the concentration values and the formula including explanatory variables to be substituted with the concentration values, to the evaluating apparatus; and

a result-receiving unit that receives an evaluation result on future risk of developing cerebral and cardiovascular events, transmitted from the evaluating apparatus, and

the control unit of the evaluating apparatus includes:

a data-receiving unit that receives the

concentration data or the value of the formula transmitted from the terminal apparatus;

an evaluating unit that evaluates future risk of developing cerebral and cardiovascular events for the subject, using the concentration values included in the concentration data or the value of the formula received by the data-receiving unit; and

a result-sending unit that transmits the evaluation result obtained by the evaluating unit to the terminal apparatus.

18. A terminal apparatus comprising a control unit,

wherein the control unit includes a result-obtaining unit that obtains an evaluation result on future risk of developing cerebral and cardiovascular events,

wherein the evaluation result is a result of evaluating future risk of developing cerebral and cardiovascular events for a subject to be evaluated, using (i) concentration values of at least two amino acids of Gly, Cit, Trp, Met, Val, His, Pro, and Tyr in blood of the subject, or (ii) a value of a formula calculated using the concentration values and the formula including explanatory variables to be substituted with the concentration values.

19. The terminal apparatus according to claim 18, being communicatively connected via a network to an evaluating apparatus that evaluates future risk of developing cerebral and cardiovascular events,

wherein the control unit includes a data-sending unit that transmits concentration data on the concentration values, or the value of the formula, to the evaluating apparatus,

the result-obtaining unit receives the evaluation

result transmitted from the evaluating apparatus.