2018

Mortality risk factors in community dwelling elderly - Knowledge base

Lucas Middeldorf Rizzo
Technological University Dublin, lucas.rizzo@tudublin.ie

Ljiljana Majnaric
University of Osijek, ljiljana.majnaric@gmail.com

Luca Longo
Technological University Dublin, luca.longo@tudublin.ie

Funder: Conselho Nacional de Desenvolvimento Científico e Tecnológico

Mortality risk factors in community dwelling elderly Knowledge base

Majnaric, Ljiljana
ljiljana.majnaric@gmail.com

Rizzo, Lucas
lucasmrizzo@gmail.com

Longo, Luca
longo.luca@gmail.com

January 31, 2018

Contents

1 Attribute description

Biomarkers, type categorical (C) or numerical (C) and short description.

Biomarker	Type	Values range
age	N	<60, 60-65, 66-70, 71-75, 76-80, >80
sex	C	F, M
hyper	C	Diagnosis of Hypertension Low-grade (<160/90 mm Hg; medications are not used, or used irregularly), High-grade (>160/90 mm Hg; medications are used regularly)
DM	C	Diagnosis of Diabetes mellitus type 2 yes, Impaired glucose tolerance, No
HbA_{1c}	N	Glycosilated Haemoglobin (%) - a marker of an average blood glucosein a three-month period Please, split the range of values into tertiles or quartiles, as appropriate
Fglu	N	Fasting glucose (mmol/L) - a marker of glucose metabolism
Chol	N	Total cholesterol Please, split the range of values into tertiles or quartiles, as appropriate
HDL	N	HDL-cholesterol Please, split the range of values into tertiles or quartiles, as appropriate
Statins	C	Statins use Yes, No
anticoag	C	Therapy with oral anticoagulant drug (warfarin), therapy with antiaggregant drug (aspirin), therapy with antiaggregant plant drug (ginkgo)
CVD	C	Cardiovascular disease. No, myocardial infarction/angina/history of revascularization, chronic myocardiopathy with atrial fibrillation, chronic myocardiopathy without atrial fibrillation, stroke/transient ischaemic cerebral event, carotid artery atherosclerosis confirmed by using image techniques, peripheral vascular disease
BMI	N	Body mass index (a measure of the body weight) <20, 20-25, 26-29, >=30
w/h	N	Weist to hip ratio - M <1.0, >=1.0; F <0.8, >=0.8
skinf	N	Triceps skinfold thickness Please, split the range of the values into tertiles, separately for M and F
COPD	C	Chronic Obstructive Pulmonary Disease – Yes, No
Aller d	C	Allergic disease (rhinitis/asthma) - Yes, No
Dr aller	C	Allergy to drugs - Yes, No
Analg	C	Long-term use of analgesics/nonsteroidal antiinflammatory drugs - Yes, No
Neo	C	No, malignant disease in a stable phase, skin malignancy
Derm	C	Chronic skin disorders Chronic dermatitis, dermatomycosis, No
OSP	C	Osteoporosis - an age-related disease affecting mostly women, characterized with increased bone fragility and susceptibility for fracture. Osteoporosis/osteopenia/no - of the radius bone; osteoporosis/osteopenia/no - of the vertebrae; osteoporosis/osteopenia/no - of the hip
Psy	C	Anxyety/depression, Parkinson‘s disease, cognitive impairment, no
MMS	N	Neuropsychologic test for screening on cognitive impairment ”Mini Mental Score” <10 severe cognitive imapirment, 10 - 20 moderate, 21 - 24 mild, 25 - 30 normal cognition
CMV	N	Cytomegalovirus infection (specific IgG antibodies, IU/ml). Please, split the range of values into tertiles, or quartiles, if appropriate
EBV	N	Epstein-Barr virus infection (specific IgG antibodies, IU/ml). Please, split the range of values into tertiles, or quartiles, if appropriate

Biomarker	Type	Values range
HPA	N	Helicobacter pylori infection (specific IgA antibodies, IU/ml). Please, split the range of values into tertiles, or quartiles, if appropriate
LE	N	White blood cell (WBC) count (Leukocytes number × 109/L). Please, split the range of values into tertiles, or quartiles, if appropriate
CRP	N	C-reactive protein (mg/L). Please, split the range of values into tertiles, or quartiles, if appropriate
GAMA	N	Hiper-gamma-globulinemia (g/L) - a marker of chronic inflammation
MO	N	Monocytes % in WBC differential. Please, split the range of values into tertiles, or quartiles, if appropriate
NEU	N	Neutrophils % in WBC differential. Please, split the range of values into tertiles, or quartiles, if appropriate
LY	N	Lymphocytes % in WBC differential Please, split the range of values into tertiles, or quartiles, if appropriate
E	N	Red Blood Cell (RBC) count (Erythrocytes number × 10^12/L) Please, split the range of values into tertiles, or quartiles, if appropriate
HB	N	Hemoglobin (g/L). Please, split the range of values into tertiles, or quartiles, if appropriate
HTC	N	Hematocrite (Erythrocyte volume blood fraction) Please, split the range of values into tertiles, or quartiles, if appropriate
MCV	N	RBC Mean Cell Volume (fL). Please, split the range of values into tertiles, or quartiles, if appropriate
FE	N	Serum iron (g/L). Please, split the range of values into tertiles, or quartiles, if appropriate
ALB	N	Serum albumin (g/L). Please, split the range of values into tertiles, or quartiles, if appropriate
Clear	N	Creatinine clearance - an indicator of chronic renal impairment (ml/s/1.73m^2) Please, split the range of values into tertiles, or quartiles, if appropriate
HOMCIS	N	Homocystein (μmol/L)- sulphuric amino-acid Please, split the range of values into tertiles, or quartiles, if appropriate
VITB12	N	Vitamin B12 (pmol/L) Please, split the range of values into tertiles, or quartiles, if appropriate
FOLNA	N	Folic acid (mM/L) Please, split the range of values into tertiles, or quartiles, if appropriate
INS	N	Serum fasting insulin (IU/ml) Please, split the range of values into tertiles, or quartiles, if appropriate
CORTIS	N	Serum cortisol in the morning (nmol/L) Please, split the range of values into tertiles, or quartiles, if appropriate
PRL	N	Prolactin in the morning (mIU/L) - the anterior pituitary gland hormone Please, split the range of values into tertiles, or quartiles, if appropriate
TSH	N	Thyroid-stimulating hormone (IU/ml) - the anterior pituitary gland hormone Please, split the range of values into tertiles, or quartiles, if appropriate
FT3	N	Free triiodothyronine (pmol/L) - the thyroid gland hormone Please, split the range of values into tertiles, or quartiles, if appropriate
FT4	N	Free thyroxine (pmol/L)- the thyroid gland hormone Please, split the range of values into tertiles, or quartiles, if appropriate
RF	N	Rheumatoid factor - the auto-antibody, increased in patients with rheumatoid arthritis In cases where RF is tested positive, please, split the range of values into tertiles, or quartiles, if appropriate
ANA	N	Anti-nuclear antibody - the auto-antibody - a diagnostic marker in rheumatic autoimmune diseases Please, split the range of values into tertiles, or quartiles, if appropriate
IGE	N	Immunoglobuline E - a class of antibody included in the allergic reactions Please, split the range of values into tertiles, or quartiles, if appropriate

2 Attribute risk description

Attribute	Description	References
age	The strongest risk factor for death. In general: the older the person, the higher the risk of death; although, due to the remodelling theory of aging, the mortality rates are the highest at the age of around 75, due to the chronic disease burden; after the age of 80, the population mortality curve starts to slowdown, reflecting the positive selection of oldest old individuals, who are also characterized with better coping mechanisms	1-2
sex	For some pathophysiological aspects of ageing, such as diabetes and metabolic syndrome, there is a presumption that men and women use different pathways to attain ageing diseases and premature mortality (or longevity)	3-4 & Presumption
hyper	Hypertension is the main risk factor for cardiovascular disease - the main mortality cause in European countries. Thus, the higher grade hypertension - the stronger association with mortality. On the other hand, persons with high grade hypertension more regularly use anti-hypertensive drugs, which may, in turn, elicit the protective effect	5-6 & Presumption & Intuition
DM	Diabetes mellitus,mostly based on the pre-existing obesity, is the main risk factor for cardiovascular disease - the main mortality cause in European countries. Thus, diabetics might have the highest mortality risk, in comparison to non-diabetics and those having pre-diabetes (impaired glucose tolerance). However, there might be an alleviating effect of drug treatment, in diabetic patients. Another contradictory argument is the fact that impaired glucose tolerance is a condition characterized with high insulin resistance and insulin serum concentrations -both factors confirmed as to have the strong impact on the development of many aging diseases. In addition, among those subjects not having diabetes, there might be some individuals characterized with frailty - another strong mortality risk factor.	7-9 & Presumption & Intuition
HbA1c	According to the above commentaries and the remodelling theory of aging, both lowered and increased values of Hba1c - a measure of blood glucose concentrations - may be detrimental for healthy aging and longevity. An intriguing is also to note that, in diabetics, the HbA1c values are under the influence of treatment	10-11 & Presumption & Intuition
FGlu	Fasting Glucose – a marker of glucose metabolism	
chol	High serum concentrations of total cholesterol is well established as the main risk factor for cardiovascular disease and, as such, it can be also associated with premature death. On the other hand, hypolipemic treatment with statins is less efficient in elderly people, which may implicate weaker influence of total cholesterol as CV risk factor, in this population group. Also, therapy with statins, mostly used by diabetics, is known to modify the total cholesterol levels.	12-13 & Presumption
HDL	High serum HDL-cholesterol concentrations (certainly ¿1.0 mmol/L) is thought to be protective against diabetes, cardiovascular disease and Alzheimer‘s dementia, so also against premature death. A conflicting fact is that recent evidence implicate not only low serum concentrations of HDL-cholesterol, but also functionally defective HDL particles, as to be detrimental for the development of age-related chronic diseases. In general, low serum HDL-cholesterol concentrations - a cardiovascular risk factor - can be expected in conditions associated with insulin resistance, including obesity, especially abdominal obesity, diabetes, hypertension, CVD, chronic renal impairment and frailty (muscle wasting).	14-15 & Presumption

Attribute	Description	References
Statins	Therapy with statins can modify the total cholesterol levels, so can be protective for premature cardiovascular disease and death. Although, recent studies indicate lower effectiveness of this therapy in elderly population. Also, there are ambiguous results in respect to statins use and the development of cognitive dysfunction/dementia -an emerging cause of death in modern societies.	13, 16-17 & Presumption
anticoag	Oral anticoagulant/antiaggregant drug treatment is a part of a secondary prevention strategy of CVD and can be a marker of higher CV risk and death. On the other hand, the effect of this therapy on CVD and average life expectancy can be beneficial. Therapy with these medications can yet be associated with potential adverse effects and serious complications. Further, there might be a difference between the effectiveness of anticoagulant and antiaggregant drugs.	18-20 & Presumption, Intuition
CVD	Cardiovascular disease is the major cause of mortality. However, there may be differences in respect to an influence of age, gender, co-morbidity, or a specific CVD entity (for example, stroke vs peripheral vascular disease)	21 & Presumption, Intuition
BMI	Evidence say that both, low values of BMI (<20) and high values (>=30), may contribute to CV and overall mortality. Overweight (BMI 26-29) may also have unfavourable effect. However, there are no clear relationships between BMI and other CV risk factors, such as lipids, hypertension and insulin resistance, as well as in respect to gender and age differences.	10,22-25 & Presumption, Intuition
w/h	Increased weist cicumference and weist to hip ratio are well established measures of insulin resistance and CV risk factors, either being associated with obesity, or frailty. The strength of associations with the risk of mortality is not well known.	25
skinf	Increased triceps skinfold thickness is validated as an anthropometric measure of insulin resistance state (muscle wasting). Data on the strengh of associations towards CVD and overall mortality are not yet conclusive.	26-27
COPD	COPD is a major cause of mortality and also a CV risk factor. There may be a survival benefit for treatment with new inhalatory drugs, however, conclusive data are currently lacking.	28
Aller d	Allergic diseases have in the background increased activity of the antibody-mediated (humoral) immune response (represented with high serum IgE concentrations). In this sense, these diseases may elicit protective effects towards CVD and premature death, as CVD and some other aging diseases, including dementia and cancer, use cell-mediated immunity during their pathogenesis. Although strong evidence are lacking, recent advances in aging process propose that the development of the main aging diseases is the result of the unsuccessful modeling, which is associated with the bias of the immune reaction into the cell-mediated and antibody-mediated immune response. In this context, the bias towards humoral (antibody-mediated) immunity is associated with the development of allergic diseases and hematoproliferative disorders. These latter disorders, in turn, may be unfavourable for survival.	1,29-32 & Presumption, Intuition
Dr aller	Drug allergy might be a marker of multimorbidity and, as such, of the complex unfavourable pathogenetic background	33 & Presumption, Intuition
Analg	Analgesics can alleviate inflammation - according to the theory - the main driving cause of age-related diseases. So, this therapy might be beneficial for survival, although it can be accompanied with the serious side effects, for example decline of renal function. Alternatively, use of these medications can be a marker of a subgroup of patients with locomotor disease in its active phase - characterized with increased level of inflammation, which, in turn, may be non beneficial for survival	18,19 & Presumption, Intuition

Attribute	Description	References
Neo	Patients in the stable phase of malignant disease, including those with skin cancer, might be in an unfavourable position in respect to survival, because of the immune system impairment. According to the recent theories of aging, unsuccessful remodelling of the metabolic, the immune and the neuro-endocrine systems is responsible for increased level of inflammation and the development of the age-related chronic diseases.	29, 34 & Presumption, Intuition
Derm	Chronic skin disorders can be a marker of the immune system dysfunction and, as such, of an unfavourable survival pattern	35 & Presumption, Intuition
OSP	Osteoporosis is an inflammation-mediated disease, so unfavourable for survival. Overt osteoporosis may be more detrimental than the disease in its early phase - osteopenia. Although, in an early phase of this disease, the level of inflammation can be even at the higher level than when the disease turns into its advanced stage. This is supported by the evidence implicating osteopenia as a component of the frailty syndrome, characterized with increased level of inflammation. Osteoporosis is a spot like disease, so the larger the number of invloved sites, the greater the influence of the disease on the survival	36-37 & Presumption, Intuition
Psy	Anxyety-depresson and cognitive disorders are all known to activate the hypothalamo-pituitary-adrenal (HPA) axis, which decreases an individual‘s adaptation to infections and illnesses, mostly due to the immune system impairment and increased secretion of inflammatory cytokines and other mediators. So, these diseases are unfavourable for survival.	38-39 & Presumption, Intuition
MMS	MMS < 25 is a measure of mild cognitive impairment (MCI) - an early phase during the course of the development of dementia . Some known factors responsible for progression of MCI to dementia include deficit of folic acid and vitamin B12, the thyroid gland hypofunction and depression/anxyety. Although not all persons with MCI get dementia, this condition is associated with the immune system bias towards the cell-mediated immunity, which may affect survival.	40 & Presumption, Intuition
CMV	Latent infections reactivation is a feature of unsuccessful aging. High serum specific IgG antibody concentrations can be used as a marker of CMV infection reactivation. This condition is a driving force for cellular immunity activation and exhaustion. High serum concentrations of specific IgG antibodies have been accepted as the risk factor for frailty and premature death.	41-42 & Presumption
EBV	High serum specific IgG antibody concentrations can be considered as a marker of the immune system impairment and bias towards B lymphocytes (humoral immunity) domination. In this sense, this condition might be beneficial for survival, by turning the immune reaction from the cellular towards the domination of humoral immunity, avoiding the development of the main aging diseases, including CVD, dementia and cancer. On the other hand, EBV infection is a driving force for the development of lymphomas and lymphoproliferative disorders, which might be unbeneficial for survival.	43 & Presumption
HPA	Helicobacter pylori infection, a cause of chronic gastritis, is a wide-spread condition in older population. Because of its association with increased systemic inflammation and biased immune reaction in favour of cell-mediated immunity, this infection might be unbeneficial for survival. Increased serum concentrations of specific IgA antibodies (>11.1 IU/ml) is a diagnostic test used to confirm this infection.	44-45 & Presumption

Attribute	Description	References
LE	Leukocyte count, a marker of inflammation, is frequently included in routine clinical checkups. According to the recent studies, increased leukocyte count, in apparently healthy elderly population, can be used as a prognostic factor of all-cause and cardiovascular mortality. Aspirin and nonsteroidal antiinflammatory drugs may lower their counts.	18, 46 & Presumption
CRP	Low grade chronic inflammation, as indicated with slightly elevated serum concentrations of CRP (even in the upper part of the reference range), has been considered as the main pathogenetic driving force in the progression of the main aging chronic diseases, including CVD, dementia, osteoporosis, cancer, autoimmune and lymphoproliferative diseases. In addition, it may also play a major role in the development of the frailty syndrome, which in older persons is associated with increased vulnerability for disease and death. Phenotipically, this syndrome is characterized with lean body mass, osteopenia, anemia and low cholesterol level. The etiology of chronic inflammation is considered to be multifactorial. One of the best accepted cause is obesity. In this condition, low grade inflammation is associated with insulin resistance and impaired glucose tolerance, increasing, in obese people, their susceptibility for diabetes and CVD. More generally, it is thought that age-related dysfunction in the metabolic, the neuroendocrine and the immune system, is associated with chronic low grade inflammation. Increased serum CRP concentrations have been found to be associated with increased risk of CV and all-cause mortality.	1,18,29,30, 47 & Presumption
GAMA	Hiper-gamma-globulinemia – a marker of chronic inflammation	
MO	Mononuclear leukocytes are included in cell-mediated immunity during pathogenesis of atherosclerotic CVD, dementia and cancer. Although monocytes % in WBC differential is a weaker marker of cell-mediated immunity than absolute monocytes number, it is more easily available in clinical practice. Some age-related changes in WBC differential, including slightly increased monocytes %, decreased lymphocytes % and increased neutrophils %, have been found as to have predict ive power in CV and all-risk mortality.	48-49 & Presumption
NEU	Some age-related changes in WBC differential, including slightly increased monocytes %, decreased lymphocytes % and increased neutrophils %, have been found as to have predict ive power in CV and all-risk mortality.	48-49 & Presumption
LY	Some age-related changes in WBC differential, including slightly increased monocytes %, decreased lymphocytes % and increased neutrophils %, have been found as to have predict ive power in CV and all-risk mortality.	48-49 & Presumption
E	Erythrocytes (RBC) number is a routine laboratory test indicating blood oxygen carrying capacity, or otherwise, used to diagnose anaemia. According to the evidence, anemia, in older persons, as indicated by lower Hemoglobin and Erythrocytes number, is associated with an increased mortality risk. On the other hand, even slightly increased erythrocytes number, due to hypoxic lung or heart diseases, can affect blood rheological properties and vascular resistance, increasing the risk for unfavourable outcomes.	50-52 & Presumption, Intuition
HB	Hemoglobin is a more sensitive marker of anemia than erythrocytes number. Both, decreased HB values (indicating anaemia) and increased HB values (corresponding with impaired blood rheology) might be unfavourable for survival.	50-52 & Presumption, Intuition
HTC	Hematocrit values depend on the number and size of red blood cells. Lower HTC may be due to anemia, or WBC hematoproliferative disorders, while increased HTC may due to increased erythrocytes number, or enlarged RBC MCV (macrocytic anemia). Extremes from both sides may be unfavourable for survival.	53-56 & Presumption, Intuition

Attribute	Description	References
MCV	The incidence of vitamin B12 and folate deficiency increases with age and may lead to macrocytosis (indicated by increased MCV). Macrocytosis may also develop as a result of age-related shortened RBCs life-span, independently of vitamin B12 and folate deficiency. These large RBCs are known to have difficulties in passing through capilary vessel network, leading to insufficient tissue supply with oxygen and nutritients. Older people with these disturbancies are more likely to have poorer cognitive functioning and increased mortality. Some subpopulations of older people are especially prone to macrocytosis, including those with chronic gastritis, chronic kidney and heart disease, as well as those with multi-morbidity.	57-60 & Presumption
FE	Testing serum iron is a part of complete blood count test. As according to the evidence, both, lower and upper extremes of the interval values, recorded in the sample, might be unbeneficial for survival.	61-62 & Presumption, Intuition
ALB	Lower serum albumin, in older people, although still within the reference range, may be a marker of low grade chronic inflammation, or more specifically, of the frailty syndrome, characterized also with lower total cholesterol, muscle wasing (energy-protein malnutrition)and anemia.	36, 63 & Presumption
Clear	Decline in renal function, indicated by increased values of creatinine clearance, is associated with a variety of pathophysiologic changes, including hypertension, insulin resistance, other metabolic changes, increased inflammation, the immune system dysfunction, protein malnutrition (muscle vasting), endocrine disorders, anemia and blood rheology. Chronic renal impairment has been recognized as the main risk factor for CVD and dementia.	64-68 & Presumption
HOMCIS	Increased serum concentrations of the amino-acid homocystein has been found to have strong oxydative properties. Increased oxydative stress is a driving force for the development of the main age-related chronic diseases. In addition, hyperhomocysteinemia is an indicator of impaired DNA methylation process and cell-cycling, which may have the greatest impact on the functioning of cells with a high cell turn-over, such as immunocompetent cells. Serum concentrations of homocystein > 12.5 μmol/L has been confirmed as the risk factor for CVD and dementia. This disorder is closely related to vitamin B12 and folic acid deficiency and frequently found in subjects with chronic renal renal impairment, especially when it is associated with increased level of inflammation and protein malnutrition.	69-71 & Presumption
VITB12	Deficiency of B-vitamins, notably of vitamin B12 and folic acid, has been confirmed as the main cause of mild hyperhomocysteinemia. The mechanism which links these disorders into the same pathogenetic network is the metabolic cycle of the amino acid methionine, an essential biochemical reaction during DNA methylation reaction. This metabolic cycle is controlled by the common set of enzymes. The activity of one of these enzymes, the methylene tetrahydrofolate reductase. is also greatly influenced by the genetic variations. Disorders associated with the impaired methylation reactions include: DNA damage, genome instability, impaired cell proliferation and insufficient neurotransmitter synthesis. These are all mechanisms during the course of the development of the age-related diseases, including atherosclerotic CVD, neurodegenerative disease nad cancer. The main causes of vitamin B12 and folic acid deficiency, in older population, include low dietary intake, impaired absorption due to chronic gastritis and oxidative depletion due to chronic renal impairment.	72-74 & Presumption
FOLNA	The same as above	72-74 & Presumption

Attribute	Description	References
INS	Increased serum insulin concentrations is a clinical marker of insulin resistance - an insufficient action of insulin on insulin-sensitive target tissues, notably muscles. Insulin resistance is a mechanism of impaired glucose metabolism associated with obesity, diabetes, frailty and chronic renal impairment. Increased serum insulin concentrations, >= 85.2 pmol/L, has been accepted as the part of the insulin resistance (Metabolic) syndrome - a cluster of clinical features including also abdominal obesity, hypertension, increased Triglycerides and/or decreased HDL-cholesterol serum concentrations. The prevalence of this syndrome increases in aging population. It is a well accepted risk factor for the development of diabetes and CVD. Recent studies also link folate deficiency, increased level of inflammation and impaired blood rheology, to the Metabolic syndrome. They also emphasize the possible gender differences in the Metabolic syndrome and its role in the development of CVD.	75-78 & Presumption
CORTIS	Serum cortisol secretion is a part of the stress-adaptive response of the hypothalamo-pituitary-adrenal (HPA) axis. This is a dynamic feedback network with circadian rhytmicity and pulsatile neurohormone secretion. The HPA axis is the main neuroendocrine pathway which regulates the immune system. Reversely, one of the most powerful stimuli of this axis is IL-6 - the main cytokine of the inflammatory response. The complex pathogenetic network, including obesity, dysregulation of the neuroendocrine stress axis, increased inflammation and insulin resistance, has been found to be a risk factor for CVD. It is not completely understood of how aging causes changes in the HPA axis. It appears that there is no deficiency of adrenal production of cortisol, but in its pulsatile and 24h rhytmic release. In older subjects, serum cortisol secretion may vary more within a 24h period, as compared to younger subjects. So, both lower and higher serum concentrations of cortisol in the morning, might be detrimental for survival. In older population, there is a close association between the HPA axis activation, depression / mood disorders and neurodegenerative disorders (corresponding with cognitive impairment and dementia). According to the recent meta-analysis, greater diurnal decline of the HPA axis (drop between the morning and evening cortisol), is associated with better physical performance in later life. Epidemiologic studies have not confirmed the role of chronic activation of the stress axis with increased mortality in later life.	79-83 & Presumption, Intuition
PRL	The role of variations in serum prolactin concentrations, in aging diseases, has not been clarified. Evidence indicate the association of increased serum prolactin concentrations with the insulin resistance syndrome, chronic inflammation, the immune system dysregulation, depression/neurodegenerative diseases and chronic renal impairment.	84-86 & Presumption
TSH	Isolated finding of mildly increased serum concentrations of the hormone TSH is a marker of subclinical form of the primary hypothyreoidism - a frequent disorder in older population. Evidence suggest the association of this disorder with decreased bone mineral density in postmenopausal women, increased cholesterol and increased risk for atrial fibrillation, while evidence are controversial on the associations with CVD, cognitive impairment and all-cause mortality. Evidence are in favour of no harmful effect of subclinical hypothyreoidism on the overall mortality in elderly. According to the evidence, hypothyreoidism and moderate subclinical hypothyreoidism (TSH > 6 IU/ml) are associated with increased CV and all-cause mortality in patients with multiple CV risk factors and clinically manifest vascular disease.	87-90 & Presumption

Attribute	Description	References
FT3	The thyroid gland hormones are rarely changed in the elderly. The most frequent patterns of changes include decreased fT3 and normal or increased fT4 - a sign of nonthyroidal illness (a peripheral tissue resistance on the action of the thyroid gland hormones due to the existence of overt chronic diseases). This pattern of the thyroid gland hormones changes is often associated with chronic renal impairment and is unbeneficial for survival.	87-90 & Presumption
FT4	The same as noted above	87-90 & Presumption
RF	Rheumatoid factor positivity can be find for years before the onset of rheumatoid arthritis and may be considered as the marker of increased CV risk.	91
ANA	Increased serum concentrations of the auto-antibody ANA can be found in healthy elderly people, but especially in association with different chronic diseases. It may be a marker of the bias of the immune reaction towards the prevalence of the antibody-mediated (humoral) immunity.	92 & Presumption
IGE	The same as noted under the allergic diseases	1,29-32 & Presumption, Intuition

3 Terms extracted and the associated risk of mortality

Risk	English description
no risk	. might be beneficial for survival . protective against premature death . may be protective
low risk	
medium low risk	. increasing the risk for unfavorable outcomes . may be non beneficial for survival . may also have unfavorable effect . well established measures of insulin resistance and CV risk factor . ... The strength of associations with the risk of mortality is not well known . may be unfavorable for survival . might be detrimental for survival . unfavorable pathogenetic background . may affect survival . might be unbeneficial for survival . may be detrimental for healthy aging and longevity . might be in an unfavorable position in respect to survival . can be expected in conditions associated with insulin resistance, diabetes, hypertension, etc.
medium risk	. may contribute to CV and overall mortality . unfavorable for survival . predictive power in CV and all-risk mortality . unbeneficial for survival . marker of increased CV risk . strong impact on the development of many aging diseases . may affect survival - severe cognitive impairment . can be a marker of higher CV risk and death unfavorable survival pattern
medium high risk	. has been confirmed as the risk factor for cvd and dementia . strong mortality risk factor . risk factor for frailty and premature death . increased risk of CV and all-cause mortality . increased cv and all cause mortality . increased mortality risk
high risk	. it is a well accepted risk factor for the development of diabetes and CVD . main risk factor for cardiovascular disease - the main mortality cause . the higher grade ... the stronger association with death . the highest mortality risk . prognostic factor of all-cause and cardiovascular mortality . main risk factor for cvd and dementia . main cause of mild hyperhomocysteinemia
extremely high risk	. major cause of mortality . major cause of mortality and also a CV risk factor . strongest risk factor

4 Laboratory normal values

Parameter	Reference ranges
Glucose (fglu)	4.4 - 6.4 mmol/L
HBA_{1c}	2.8 – 3.8 %
Total cholesterol	3.5 - 5.2 mmol/L
Triglycerides	0.5 - 1.8 mmol/L
HDL-cholesterol	0.9 - 1.4 mmol/L
IgG Antibodies on cytomegalovirus	until 0.4 IU/ml
IgG antibodies Helicobacter pylori	> 11 IU/ ml
IgA antibodies Helicobacter pylori	> 11 IU/ ml
Total Leukocytes	3.4 - 10.0 × 109/L
(%) neutrophiles	44.0 - 72.0 %
(%) Monocytes	2 - 12 %
(%) Lymphocytes	20 - 46 %
C-reactive protein	do 5.0 mg/L
Erythrocytes	4.34 - 5.72 × $10^1$2/L
Haemoglobin	138 - 175 g/L
MCV	83.0 - 97.2 fL
Serum ferum	11.0 - 32.0 μmol/L
Serum albumine	35 - 52 g/L
Clearance	1.6 - 2.94 ml/s/1.73m^2
Homocisteine	5,0 – 15,0 μmol/L
γ-globuline (GAMA)	7.6- 1 6.5 g/L
Vitamine B12	128 – 648 pmol/L
Folna (folic acid)	6 - 39 mM/L
Serum Cortisol (in the morning)	154 -638 nmol/L
Prolactin	M 65.7 - 439.8, F 76.3 - 400.7 mIU/L
TSH	0,46 – 4,68 Ul/ml
fT3	4.26 - 8.10 pmol/L
fT4	10 - 28.2 pmol/L
Anti- nuclear Antibodies (ANA)	until 23 μIU/ml
IgE antibodies	<114 kIU/L

5 Forecast arguments

This section provides an associated risk by attributes in isolation. It is important to give an importance value to each of this rules so we know how important these are in comparison with the loops.

R1. **Age**

- $< 60 \rightarrow$ `low risk`
- $[60, 65] \rightarrow$ `medium low risk`
- $[66, 70] \rightarrow$ `medium risk`
- $[71, 75] \rightarrow$ `high risk`
- $[76, 80] \rightarrow$ `extremely high risk`
- $> 80 \rightarrow$ `medium risk`

R2. **Hyper**

- $no \rightarrow$ `low risk`
- $yes \rightarrow$ `high risk`

R3. **DM**

- $yes \rightarrow$ `high risk`
- $IGT \rightarrow$ `medium risk`

R4. **HbA1c**

- < 2.8 OR $> 3.8 \rightarrow$ `medium low risk`

R5. **Chol**

- > 5.18 AND $< 6.19 \rightarrow$ `medium risk`
- $>= 6.19 \rightarrow$ `high risk`

Source: `https://medlineplus.gov/magazine/issues/summer12/articles/summer12pg6-7.html`

R6. **HDL**

- $> 1.0 \rightarrow$ `no risk`
- $< 1.0 \rightarrow$ `medium-low risk`

R7. **Statins**

- yes AND $chol > 5.18 \rightarrow$ `low risk`

R8. **Anticoag**

- $yes \rightarrow$ `medium risk`

R9. **CVD**

- $yes \rightarrow$ `extremely high risk`

R10. **BMI**

- < 20 OR $>= 30$ OR $[26, 29] \rightarrow$ `medium risk`

R11. **w/h**

- > 1 AND $male \rightarrow$ `medium low risk`
- > 0.8 AND $female \rightarrow$ `medium low risk`

R12. **COPB**

- $yes \rightarrow$ `extremely high risk`

R13. **Aller d**

- $yes \rightarrow$ `no risk`

Importance [0, 100]:

1. **Dr allerg**
   - $yes \rightarrow$ `medium low risk`

R14. **Analg**

- $yes \rightarrow$ `low risk`

R15. **Neo**

- $yes \rightarrow$ `medium low risk`

R16. **Derm**

- $yes \rightarrow$ `medium low risk`

R17. **OSP**

- $yes \rightarrow$ `medium risk`

R18. **PSY**

- $yes \rightarrow$ `medium risk`

R19. **MMS**

- $< 10 \rightarrow$ `high risk`
- $>= 10$ AND $< 25 \rightarrow$ `medium low risk`

R20. **CMV**

- $> 8.1 \rightarrow$ `medium high risk`

Source: `https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2877470/`

R21. **HPA**

- $> 11.1 \rightarrow$ `medium low risk`

R22. **LE**

- men AND $> 6.8 \rightarrow$ `medium risk`
- $women$ AND $> 6.5 \rightarrow$ `medium risk`

Source: https://www.hindawi.com/journals/jar/2014/475093/

R23. **CRP**

- $> 3 \rightarrow$ medium high risk

Source: http://eurheartj.oxfordjournals.org/content/31/13/1624.long

R24. **MO**

- $> 8.6 \rightarrow$ medium risk

Source: Last quartile of the dataset and attribute description.

R25. **Ly**

- $> 40 \rightarrow$ medium risk
- $< 20 \rightarrow$ medium high risk

R26. **E**

- *men* AND $< 4.52 \rightarrow$ medium high risk
- *woman* AND $< 4.10 \rightarrow$ medium high risk
- *men* AND $> 5.9 \rightarrow$ medium low risk
- *womann* AND $> 5.10 \rightarrow$ medium low risk

Source: http://emedicine.medscape.com/article/2054474-overview

R27. **Hb**

- *men* AND (< 140 OR > 175) $\rightarrow$ medium low risk
- *women* AND (< 123 OR > 153) $\rightarrow$ medium low risk

Source: http://emedicine.medscape.com/article/2085614-overview

R28. **HTC**

- $> 0.44 \rightarrow$ medium low risk
- *men* AND $< 0.42 \rightarrow$ medium low risk
- *women* AND $< 0.38 \rightarrow$ medium low risk

Source: http://hyper.ahajournals.org/content/60/3/631.long

R29. **MCV**

- $> 96 \rightarrow$ medium risk

Source: https://emedicine.medscape.com/article/2085770-overview

R30. **ALB**

- $< 35 \rightarrow$ medium high risk

Source: Laboratory normal values

R31. **Clear**

- *men* AND $< 2.08 \rightarrow$ high risk
- *women* AND $< 1.58 \rightarrow$ high risk

R32. **HOMCIS**

- $> 12.7 \rightarrow$ medium high risk

R33. **VITB12**

- $< 258 \rightarrow$ medium low risk

Source: doi:10.1177/1741826711424568

R34. **FOLNA**

- $< 11.4 \rightarrow$ medium high risk

Source: doi:10.1177/1741826711424568

R35. **INS**

- $> 12.26 \rightarrow$ medium high risk

Source: https://doi.org/10.2337/dc11-1657

R36. **CORTIS**

- < 193.3 OR $> 772.52 \rightarrow$ medium low risk

Source: http://emedicine.medscape.com/article/2088826-overview

R37. **PRL**

- *men* AND $> 439.8 \rightarrow$ medium risk
- *women* AND $> 400.7 \rightarrow$ medium risk

Source: https://doi.org/10.1093/eurheartj/ehs233

R38. **TSH**

- CVD *yes* AND $> 6 \rightarrow$ `medium high risk`

Source: `https://doi.org/10.1093/eurheartj/ehs233`

R39. **FT3**

- $< 4.26 \rightarrow$ `medium risk`

Source: `doi:10.1093/ndt/gfu024`

R40. **FT4**

- < 14 AND $FT3 < 4.26 \rightarrow$ `medium risk`

Source: `doi:10.1093/ndt/gfu024`

R41. **RF**

- $> 60 \rightarrow$ `medium risk`

Source: `doi:10.1136/ard.2009.110536`

R42. **ANA**

- $> 32 \rightarrow$ `medium low risk`

Source: last quartile of dataset and attribute description.

R43. **IGE**

- $> 114 \rightarrow$ `no risk`

Source: `doi:10.1007/s10552-014-0489-9`

R44. **FE**

- < 10.9 OR $> 18 \rightarrow$ `medium low risk`

Source: first and last quartile of dataset and attribute description

6 Preferences

Preferences over pairs of attributes.

1. Age > important than sex
2. Hyper > sex
3. Hyper > age
4. DM > hyper
5. DM > age
6. Chol = HDL
7. FGlu = HbA1c
8. Anticoag > statins
9. CVD > BMI
10. CVD > hypert
11. CVD > age
12. CVD > Neo
13. w/h > BMI
14. skinf > BMI
15. COPB > aller d
16. Dr aller > aller d
17. Analg = CRP
18. Analg > Derm
19. Neo > Derm
20. OSP > Neo
21. OSP > aller d
22. OSP > BMI
23. Psy > Derm
24. MMSE > Psy
25. CMV = EBV
26. HPA > LE
27. HPA = MCV
28. CRP > LE
29. MO > LE
30. LY > LE
31. HTC > HB
32. E=HB
33. VITB12 = MCV
34. VITB12 = FOLNA
35. Skinf > ALB
36. MMSE = VITB12
37. w/h > INS
38. HOMCIS > Clear
39. Clear > Derm
40. Clear > Aller d
41. Clear > BMI
42. HOMCIS = PRL
43. Clear > age
44. PRL > CORTIS
45. PRL=TSH
46. TSH > Chol
47. TSH = FT3
48. RF < CVD
49. CRP > ANA
50. ANA = GAMA
51. IGE = Aller d

6.1 Attacks based on preferences

1. R2 ⇒ R1
2. R3 ⇒ R2
3. R3 ⇒ R1
4. R8 ⇒ R7
5. R9 ⇒ R10
6. R9 ⇒ R2
7. R9 ⇒ R1
8. R9 ⇒ R16
9. R11 ⇒ R10
10. R12 ⇒ R13
11. R14 ⇒ R13
12. R15 ⇒ R17
13. R16 ⇒ R17
14. R18 ⇒ R16
15. R18 ⇒ R13
16. R18 ⇒ R10
17. R19 ⇒ R17
18. R20 ⇒ R19
19. R22 ⇒ R23
20. R24 ⇒ R23
21. R25 ⇒ R23
22. R26 ⇒ R23
23. R29 ⇒ R28
24. R11 ⇒ R36
25. R33 ⇒ R32
26. R32 ⇒ R17
27. R32 ⇒ R13
28. R32 ⇒ R10
29. R32 ⇒ R1
30. R38 ⇒ R37
31. R39 ⇒ R5
32. R9 ⇒ R42
33. R24 ⇒ R43

7 Contradictions

These are contradictions between attributes that might invalidate the use of one attribute.

1. If `Age` $>$ 60 then `Aller d` can not exist
2. If (`Age` $<$ 60 AND *not* `DM` AND *not* `Hyper`) OR (`Age` between 61 and 65) then `Clear` is not *low*
3. If `Clear` is *low* then `HOMCIS` is *not low*
4. If `Clear` is *low* then `PRL` is *not low*
5. If `Clear` is *low* then `TSH` is *not low*
6. If `VITB12` is *not low* then `MCV` can *not be increased*
7. If `COPB` then `Aller d` can not exist
8. If `INS` is *low* then `w/h` can *not be high*
9. If *no* `CVD` then *no* `Anticoag`
10. If *low* `Chol` then *no* `Statins`
11. If `OSP` then `CRP` can *not be low*
12. If `CVD` then *increased* `Skinf`
13. If `BMI` is *high* than `Skinf` can *not be increased*
14. If `CVD` than `Skinf` can *not be low*
15. If `MMSE` $>=$ 25 then `TSH` can *not be increased*
16. If `HOMCIS` is *low* than `Clear` can *not be low*
17. If `Chol` is *high* than `HTC` can *not be low*
18. If `IGE` *low* than `HPA` is *not high*
19. If `Clear` is *low* AND *high* `CRP` then *low* `ALB`.

20. If `VITB12` is *high* then `MCV` can *not be increased*

21. If *high* `HPA` then *low* `VITB12`

22. If `INS` is *low* then `HDL` is *not low*

23. If `DM` than `BMI` can *not be high*

24. If `DM` than `BMI` can be *high*
    Impact loops: Not implemented. 23 and 24 contradict each other.

25. If `DM` then `w/h` can *not be low*

26. If `COPB` than `Skinf` can *not be low*

8 References

1. Vasto S., Candore G., Balistreri C.R., Caruso M., Colonna-Romano G., Grimaldi M.P., et al (2007). Inflammatory networks in ageing, age-related diseases and longevity. Mech Ageing Dev, 128 (1), 83-91.

2. Manton K.G. (1999). Dyamic paradigms for human mortality and aging. The Journal of Gerontol, 54, 247-254.

3. Onat A, Hergenc G, Keles T, et al (2005). Sex difference in development of diabetes and cardiovascular disease on the way from obesity and metabolic syndrome. Metabolism 54 (6): 800-808.

4. Franceschi C., Motta L., Valensin S., Rapisarda R., Franzone A., Berardelli M., et al (2000). Do men and women follow different trajectories to reach extreme longevity? Italian multicenter study on centenarians (IMUSCE). Aging (Milano), 12 (2), 77-84.

5. Leitschuh M, Cupples LA, kannel W, Gagnon D, Chobanian A (1991). High-normal blood pressure progression to hypertension in the Framingham heart study. Hypertension 17: 22-27.

6. Goldman L, Phillips KA, Coxson P, Goldman PA, Williams L, Hunink MG (2001). The effect of risk factor reductions between 1981 and 1990 on coronary heart disease incidence, prevalence, mortality and cost. J Am Coll Cardiol 38: 12-17.

7. The Task Force on Diabetes and Cardiovascular Diseases of the European Society of cardiology (ESC) and the European association for the Study of Diabetes (EASD): Guidelines on diabetes, pre-diabetes and cardiovascular diseases: full text. (2007). European Heart Journal. Doi:10.1093/eurheart/ehl261.

8. Umegaki H. Type 2 diabetes as a risk factor for cognitive impairment: current insights. Clinical Interventions in Aging 2014; 9: 1011-1019. Dovepress. Open access.

9. Phan H.M., Alpert J.S., Fain M. (2008). Frailty, inflammation and cardiovascular disease: evidence of a connection. Am J Geriatr Cardiol, 17 (2), 101-107.

10. Paolisso G., Barbieri M., Bonafe M., Franceschi C. (2000). Metabolic age modelling: the lesson from centenarians. European Journal of Clinical Investigation, 30, 888-894.

11. Currie CJ, Peters JR, Tynan A, Evans M, Heine RJ, Bracco OL, Zagar T, Poole CD (2010). Survival as a function of HbA1c in people with type 2 diabetes: a retrospective cohort study. The Lancet 375 (9713): 481-489.

12. The Emerging Risk Factors Collaboaration. Major lipids, apolipoproteins and risk of vascular disease (2009). JAMA 302: 1993-2000.

13. ESC/EAS Guidelines for the management of dyslipidaemias (2011). Eur Heart J 32 (14): 1769-17818.

14. He Rye KA; Bursill CA, Lambert G, Tabet F, Barter PJ (2009). The metabolism and antiatherogenic properties of HDL. J Lipid Res 50: S195-S200.

15. Kontush A, Chapman J (2006). Functionally defective high-density lipoprotein: a new therapeutic target at the crossroads of dyslipidemia, inflammation and atherosclerosis. Pharmacol Reviews 58: 342-374.

16. Swiger KJ, Manalac RJ, Blumenthal RS, Blaha MJ, Martin SS (2013). Statins and cognition: a systematic review and meta-analysis of short- and long term cognitive effects. Mayo Clinic Proceedings 88 (11): 1213-1221.

17. Alzheimer‘s Association. Alzheimer‘s disease facts and figures (2009). Alzheimer‘s Dementia 5: 234-270.

18. Shoelson SE, Lee J, Goldfine AB (2006). Inflammation and insulin resistance. The Journal of Clinical Investigation 116 (7): 1793-1801. Doi:10.1172/JCI29069.

19. Berk M, Dean O, Drexhage H, McNeil JJ, Moylan S, O'Neil A, Davey CG, Sanna L, Maes M (2013). Aspirin: a review of its neurobiological properties and therapeutic potential for mental illness. BMC Medicine 11/14. Doi:10.1185/1741-7015-11-74

20. Harder S, Thurmann P (1996). Clinically important drug interactions with anticoagulants. An update. Clin Pharmacokinet 30 (6): 416-44.

21. American Heart Association (2007). Heart disease and stroke statistics-2007 update. A report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation (115):e69-e171.http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.106.179918

22. Laman-Fava S, Wilson P WF, Schaefer EJ (1996). Impact of BMI on coronary heart disease risk factors in men and women. The Framingham Offspring Study. Atherosclerosis, Thrombosis and Vascular Biology 16: 1509-1515. Doi: 10.1161/01.ATV.16.12.1509

23. Anstey KJ, Cherbuin N, Budge M, Young J (2011). Bodx mass index in midlife and late-life as a risk factor for dementia: a meta-analysis of prospective studies. Obesity reviews 12: e426-e437. Doi: 10.1111/j.1467-789X.2010.00825.x

24. St-Pierre AC, Cantin B, Mauriege P, Bergeron J, Dagenais GR, Despres J-P, Lamarche B (2005). Insulin resistance syndrome, BMI and the risk of ischaemic heart disease.CMAJ 172 (10):1301-1305. DOI:10.1503/cmaj.1040834

25. Klein S, Allison DB, Heymsfield SB, Kelley DE, Leibel RL, Nonas C, Kalm R (2007). Waist circumference and cardiometabolic risk. A consensus Statement from Shaping America's Health: Association for Weight Management and Obesity Prevention; NAASO, The Obesity Society; The American Society for Nutrition; and the American Diabetes Association. Diabetes Care 30 (6): 1647-1652.

26. Sievenpiper JL, Jenkins DJA, Josse RG, Leiter LA, Vuksan V (2001). Simple skinfold-thickness measurements complement conventional anthropometric assessments in predicting glucose tolerance. Am J Clin Nutr 73: 567-573.

27. Cuppari L, Meireles MS, Ramos CI, Kamimura MA (2004). Subjective Global Assessment for the Diagnosis of Protein-Energy Wasting in Nondialysis-Dependent Chronic Kidney Disease Patients. J Ren Nutr pii: S1051-2276(14)00094-6.doi: 10-1053/j.jm.2014.05.004.

28. Mannino DM, Kiri VA (2006). Changing the burden of COPD mortality. Int J Chron Obstruct Pulmon Dis 1 (3): 219-233.

29. Franceschi C., Valensin S., Bonafe M., Paolisso G., Yashin A.I., Monti D., et al (2000). The network and the remodeling theories of aging: historical background and new perspectives. Exp Gerontol, 35 (6-7), 879-896.

30. Vasto S., Candore G., Balistreri C.R., Caruso M., Colonna-Romano G., Grimaldi M.P., et al (2007). Inflammatory networks in ageing, age-related diseases and longevity. Mech Ageing Dev, 128 (1), 83-91.

31. Salo PM, Calatroni A, Gergen PJ, Hoppin JA, Sever ML, Jaramillo R, Arbes SJ Jr, Zeldin DC. Allergy-related outcomes in relation to serum IgE: results from the National Health and Nutrition Examination Survey 2005-2006. J Allergy Clin Immunol 2011; 127: 1226. doi: 10.1016/j.jaci.2010.12.1106

32. Abbas AK, Murphy KM, Sher A. Functional diversity of helper T lymphocytes. Nature 1996; 383: 787-793.

33. Calderon-Larranaga A, Pobladar-Plau B, Gonzales-Rubio F, Gimen-Feliu LA, Abad-Diez JM, Prados-Torres A. (2012). Multimorbidity, polypharmacy, referals and adverse drug events: are we doing well? Br J Gen Pract 62 (605): e821-826. doi: 10.3399/bjgp12X659295.

34. Schreiber RD, Old Lj, Smyth MJ. Cancer immuno-editing: integrating immunity's roles in cancer supression and promotion. Science 2011; 331 (6024): 1565-1570.

35. Castle CS (2000). Clinical relevance of age-related immune dysfunction. Clin Infect Dis 31: 578-585.

36. Ershler, W.B., Keller, E.T. (2000). Age-associated increased interleukin-6 gene expression, late-life diseases and frailty. Ann Rev Med, 51, 245-270.

37. Ginaldi L, Benedetto MC, De Martinis M (2005). Osteoporosis, inflammation and ageing. BMC Immunity & Aging 2:14. Doi:10.1186/1742-4933-2-14

38. Marques-Deak A, Cizza G, Sternberg E (2005). Brain-immune Interactionc and disease susceptibility. Mol Psyciatry 10: 239-250.

39. Anisman H, Merali Z (2003). Cytokines, strress and depressive illness: brain-immune interactions. Ann Med 35 (1): 2-11.

40. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangolas EG, Kokmen E, Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 1999; 56: 303-308.

41. Wikby A, Johansson B, Olsson J, Lofgren S, Nilsson BO, et al. (2002) Expansions of peripheral blood CD8 T-lymphocyte subpopulations and an association with cytomegalovirus seropositivity in the elderly: the Swedish NONA immune study. Exp Gerontol 37: 445–453. doi: 10.1016/s0531-5565(01)00212-1

42. Wang GC, Kao WH, Murakami P, Xue QL, Chiou RB, et al. (2010) Cytomegalovirus infection and the risk of mortality and frailty in older women: a prospective observational cohort study. Am J Epidemiol 171: 1144–1152. doi: 10.1093/aje/kwq062

43. Copie-Bergman C, Niedobitek G, Mangham DC, Selves J, Baloch K, Diss TC, et al (1997). Epstein-Barr virus in B-cell lymphomas associated with chronic suppurative inflammation. J Pathol, 183 (3), 287-292.

44. Taylor JM, Ziman ME, Canfield DR, Vajdy M, Solmick JV (2008). Effects of a Th1 versus Th2 biased immune response in protection against Helicobacter pylori challenge in mice. Microb Pathog 44 (1): 20-27.

45. Neri M, Reale M, Di Febbo C, Festi D, Calafiore AM, Conti P et al (1996). Increased levels of soluble tumour necrosis factor receptor I (sTNF RI) in serum of Helicobacter pylori – positive ischaemic heart disease patients. Gastroenterology 110: A209.

46. Nilsson G, Hedberg P, Ohrvik J (2014). White blood cell count in elderly is clinically useful in predicting long-term survival. Journal of Aging Research. Hindawi Publishing Corporation. Article ID 475093. http://dx.doi.org/10.1155/2014/475093

47. Zacho J, Tybjaerg-Hansen A, Nordestgaard BG (2010). C-reactive protein and all-cause mortality – the Copenhagen City Heart Study. European Heart Journal 31: 1624-1632. Doi:10.1093/eurheartj/ehq103

48. Kim KI, Lee J, Heo NJ, Kim S, Chin HJ, Na KY, Chae DW, Kim CH, Kim S (2013). Differential white blood cell count and all-cause mortality in the Korean elderly.Exp Gerontol 48 (2): 103-8. doi: 10.1016/j.exger.2012.11.016.

49. Shah N, Parikh V, Patel N, Badheka A, Deshmukh A, Rathod A, Lafferly J (2014). Neutrophil lymphocyte ratio significantly improves the Framingham risk score in prediction of coronary heart disease mortality: Insights from the National Health and Nutrition Examination Survey III. International Journal of Cardiology 171 (3): 390-397.

50. Izaks GJ, Westendorp RGJ, Knook DL (1999). The definition of anaemia in older persons. JAMA 281: 1714-1717.

51. Replogle RL, Meiselman HJ, Merrill EW (1967). Clinical implications of blood rheology studies. Circulation 36: 148-160. Doi: 10.1161/01.CIR.36.1.148

52. Hung WW, Wisnivesky JP, Siu AL, Ross JS. Cognitive decline among patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2009; 180: 134-137. DOI: 10.1164/rccm.200902-0276OC

53. Paul L, Jeemon P, Hewitt J, McCallum L, Higgins P, Walters M, et al (2012). Hematocrit predists long-term mortality in a non-linear and sex-specific manner in hypertensive adults. Hypertension 60: 631-638. Doi: 10.1161/HYPERTENSIONAHA.112.191510

54. Kunnas T, Solakivi T, Huuskonen K, Kalela A, Renko J, Nikkeri ST (2009). Hematocrit and the risk of coronary heart disease mortality in the TAMRISK Study, a 28-year follow up. Prev Med 49 (1): 45-47. Doi: 10.1016/j.ypmed.2009.04.015. Epub 2009 May 3.

55. Kenyeres P, Juricskay I, Tarsaly P, Keswarky G, Muhl D, Toth K, Bogar L (2008). Low hematocrit per blood viscosity ratio as a mortality risk factor in coronary heart disease. Clinicalhemorrheology and microcirculation 38 (1): 51-56.

56. Madjid M, fatemi O (2013). Components of the complete blood count as risk predictors for coronary heart disease: in-depth review and update. Texas Heart Institute Journal 40 (1): 17-29.

57. Lanu AP, Gundobalu K, Sridharan A, Jain R, Msaonel P, Chrysofakis G, et al (2013). Multiplicative interaction between mean corpuscular volume and red cell distribution width in predicting mortality of elderly patients with or without anaemia. Am J Hematol 88 (1): E245-249. Doi: 10.1002/ajh23529.

58. Gamaldo AA, Ferrucci L, Rifkind J, Longo DL, Zonderman AB (2013). The relationship between Mean Corpuscular Volume and cognitive performance in older adults. J Am Geriatr Soc 61 (1): 84-89. Doi: 101111/jgs.12066

59. Tennankare KK, Saraku SD, West KA, Kiberel BA (2011). Macrocytosis may be associated with mortality in chronic hemodyalisis patients: a prospective study. BMC Nephrology 12: 19. Doi: 10.1186/1471-2369-12-19

60. Sipponen P, Laxen F, Huotari K, Harkonen M (2003). Prevalence of low vitamin B12 and high homocysteine in serum in an elderly male population: association with atrophic gastritis and Helicobacter pylori infection. Scand J Gastroenterol 38 (12): 1209-1216.

61. Stevens RG, Graubard BI, Micozzi MS, Neriishi K, Blumberg BS (1994). .Moderate elevation of body iron level and increased risk of cancer occurrence and death. Int J Cancer 56:364-369.

62. Corti M-Ch, Guralnik JM, Salive ME, Ferrucci L, Pahor M, Wallace RB, Hennekens CH (1997). Serum iron level, coronary artery disease and all-cause mortality in older men and women. Am J Cardiol 1997: 120-127.

63. Ramadori G, Christ B (1999). Cytokines and the hepatic acute-phase response. Sem Liv Dis 19 (2): 141-155.

64. A. Davey, M. F. Elias, M. A. Robbins, S. L. Seliger, G. A. Dore (2012). Decline in renal functioning is associated with longitudinal decline in global cognitive functioning, abstract reasoning and verbal memory. Nephrology Dialysis Transplantation DOI: 10.1093/ndt/gfs470

65. Brimble KS, McFarlane A, Winegard N, Crowther M, Churchill DN (2006). Effects of chronic kidney disease on red blood cell rheology. Clin Hemorrheol Microcirc 34 (83): 411-420.

66. Kato S, Chmielewski M, Honda H, Pecoits-Filho R, Matsuo S, Yuzawa Y, et al (2008). Lindholm B. Aspects of immune dysfunction in end-stage renal disease. Clinical Journal of the American Society of Nephrology 3(5): 1526-1533.

67. S. Kobayashi, K. Maesato, H. Moriya, T. Ohtake, and T. Ikeda (2005). Insulin resistance in patients with chronic kidney disease. American Journal of Kidney Diseases 45 (2): 275–280.

68. D. Fouque, K. Kalantar-Zadeh, J. Kopple et al (2008). A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease. Kidney International 73 (4): 391–398.

69. Kuo HK, Sorond FA, Chen JH, Hashmi A, Milberg WP, Lipsitz LA (2005). The role of homocysteine in multisystem age-related problems: a systematic review. J Gerontol A Biol Med Sci 60 (9): 1190-11201.

70. Fenech MF, Dreosti IE, Rinaldi JR (1997). Folate, vitamin B12, homocysteine status and chromosome damage rate in lymphocytes of older men. Carcinogenesis 18 /7): 1329-1336.

71. Reutens S, Sachdev P (2002). Homocysteine in neuropsychiatric disorders of the elderly. Int J Geriatr Psychiatry 17 (9): 859-864.

72. Postiglione A, Milan G, Ruocco A, Gallota G, Guitto G, Di Minno G (2001). Plasma folate, vitamin B12 and total homocysteine and homozygosity for the C677T mutation of the 5,10-methylene tetrahydrofolate reductase gene in patients with Alzheimer‘s dementia. Gerontology 47 (6): 324-329.

73. Coppen A, Bolander-GouailleC (2005). Treatment of depression: time to consider folic acid and vitamin B12. Psychopharmacol 19 (1): 59-65.

74. Fuchs D, Jaeger M, Widner B, Wirleitner B, Artner-Dworzak E, Leblhuber F (2001). Is hyperhomocysteinemia due to the oxidative depletion of folate rather than to insufficient dietary intake? Clin Chem Lab Med 39 (8): 691-694.

75. International Diabetes Federation. The IDF consensus worldwide definition of the Metabolic Syndrome (2006). `www.idf.org/webdata/does/IDF_Meta_def_final.pdf`

76. Festa A, D‘Agostino R, Howard G, et al (2000). Chronic subclinical inflammation as part of the insulin resistance syndrome. Circulation 102: 42-47.

77. Regitz-Zagrosek V, Lehmkuhl E, Weickert Mo (2006). Gender differences in the metabolic syndrome and their role for cardiovascular disease. Clin Res Cardiol 95 (3): 136-147.

78. Schneider MP, Schlaich MP, Harazy JM, et al (2011). Folic acid treatment normalizes NOS-dependence of vascular tone in the metabolic syndrome obesity (Silver Spring) 19 (5): 960-967. Doi: 10.1038/oby.2010.210.Epub 2010 Sep 23.

79. Bergendhal M, Iranmanesht A, Mulligan T, Veldhmis JD (2000). Impact of age on cortisol secretory dynamics basally and as driven by nutritient-withdrawal stress. J CLin Endocrinol Metab 85 (6): 2203-2214.

80. Chahal HS, Drake WM (2007). The endocrine system and aging. J of Pathology 211: 173-180. DOI: 10.1002/path.2110

81. Swaab DF, Bao Ai-Min, Lucassen PJ (2005). The stress system in the human brain in depression and neurodegeneration. Ageing Research Reviews 4: 141-194. www.elsevier.com/locate/ar

82. Gardner MP, Lightman S, Layer AA, Cooper C, Cooper R, Deeq D, et al (2013). Dysregulation of the HPA stress axis and physical performance at older ages: an individual participant meta-analysis. Psychoneuroendocrinology 38 81): 40-49.

83. Nielsen NR, Kristensen TS, Schnober P, Gronbaek M (2008). Perceived stress and cause-specific mortality among men and women: results from a prospective cohort study. American J of Epidemiology 168 (5): 481-491. DOI: 10.1093/aje/kwn157

84. Balbach L, Wallaschofski H, Volzke H, Nauck M, Dorr M, Haring R (2013). Serum prolactin concentrations as risk factor of metabolic syndrome or type 2 diabetes? BMC Endocrine Disorders 13: 12. http://www.biomedcentral.com/1472-6823/13/12

85. Brand JM, Frohn C, Cziupka K, Brockmann C, Kirchner H, Luhm J. Prolactin triggers pro-inflammatory immune response in peripheral immune cells. Eur Cytokine Netw 15(2): 99-104.

86. Magri F, Locatelli M, Balza G, Molla G, Cuzzoni G, Fioravanti M, et al (1997). Changes in endocrine circadian rhythms as markers of physiological and pathological brain aging. Chronobiol Int 14 (4): 385-396.

87. Gesing A, Lewinski A, Karbownik-Lewinska M (2012). The thyroid gland and the process of aging, what is new? Thyroid Research 5:16. doi: 10.1186/1756-6614-5-16.

88. Donangelo I, Braunstein GD (2011). Update on subclinical hyperthyreoidism. Am Fam Physician 83 (8): 933-938.

89. Westerink J, van der Graaf Y, Faber DR, Sparing W, Wisseren FL (2012). Relation between thyroid stimulating hormone and the occurrence of CV events and mortality in patients with manifest vascular diseases. Eur J Rev Cardiol 19(4): 864-873. Doi: 10.1177/1741826711416045.

90. McQuade C, SKugor M, Brennann DM, Hoar B, Stevenson C, Hoagwert BJ (2011). Hypothyreoidism and moderate subclinical hypothyreoidism are associated with increased all-cause mortality independently of coronary heart disease risk factors: a preCIS database study. Thyroid 21 (8): 837-843. doi: 10.1089/thy.2010.0298.

91. Cavagno L, Boffini N, Cagnotto G, et al (2012). Atherosclerosis and rheumatoid arthritis: more than a simple association with mediators of inflammation. Article ID 147354.doi:10.1155/2012/147354

92. Grainger DJ, Bethell HW (2002). High titres of serum antinuclear antibodies, mostly directed against nucleolar antigens, are associated with the presence of coronary atherosclerosis. Ann Rheum Dis, 61 (2), 110-114.