Review Article

Quest for Biomarkers of Positive Health: A Review

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Abstract

The positive health of a person can be defined as the ability to live long in good health, possibly with no activity limitation. No method is yet available for its objective assessment in individuals, and we propose a framework in this communication that can operationalize this concept. Instead of distal factors, such as diet and lifestyle because these are subjective and difficult to measure, we concentrate on the objectively measurable biomarkers such as immunity level, endorphins, and handgrip strength. The focus is on the major parameters that may protect from diseases and infirmity and can be assessed by noninvasive methods. A combination of such parameters may signify positive health. This may be a novel way to measure positive health at the individual level. In this communication, we briefly review the literature and identify a few major biomarkers that provide a protective shield and could determine the status of positive health at the individual level. This exercise demonstrates that the assessment of the positive health of a person is feasible. A scale based on these and other relevant parameters can be developed later that could quantitatively measure the exact level of positive health. As the exact combination of the parameters that protects from ailments is not fully known yet, a framework such as this may help in identifying the data gaps that require attention in this context. The proposed framework may initiate a discussion on indicators of positive health and characterize the parameters for intervention that could increase a healthy life.

Keywords: Biomarkers, health assessment, health promotion, positive health, protection of health, review

Introduction

Health as a "complete physical, mental and social well-being" is an unattainable ideal and may be a mirage as the goalposts shift when an achievement is made. Public health professionals have been working on this concept at the population level,[1] but we focus in this communication on the positive health of the individuals. The concept of positive health of individuals and its domains have been described as the capability to remain healthy in the face of adversities and be able to successfully fight the ailment before its onset if it strikes.[2] In this communication, we dilate this concept with details of the domains and the specification of major biomarkers within each domain that can objectively measure the positive health of the individuals.

We do not consider distal factors such as genes, stress, nutrition, exercise, sleep, and social interactions for assessing positive health because these are mostly complex, volatile, and defy direct measurement. There is enough evidence that such distal factors modulate proximal parameters that can be objectively measured. For example, genes are involved in hormonal signaling,[3] exercise reduces the level of the body's stress hormones such as cortisol and adrenaline and stimulates the production of endorphins,[4] nutrition modulates immune functions,[5] and sleep influences cardiovascular endocrine and thermoregulatory system.[6] Thus, the positive health of a person can be directly measured by a battery of biomarkers, and such measurements will provide a much more objective assessment in a novel way. The identification and measurement of these biomarkers can help develop an effective decision-making support system for improving the health of the people and may help develop a scoring system. At the very least, this may initiate a discussion on individual-level

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indicators of positive health and characterize the parameters for intervention that could increase the healthy life.

Positive health

The concept of positive health has been around for a century although not in the form we now propose to present. The earliest reference we could locate appeared in 1924 when "positive health" was described as a double positive since health itself is a positive term.[7] The first use of the term in nearly the same sense we now discuss appeared in 2001 that described positive health as "the ability to cope with biological, psychological, and social stress" with parameters such as pain tolerance and vital capacity as the example of its indicators.[8] In 2008, it was proposed as a combination of 'excellent' status on biological, subjective, and functional measures.[9] In 2011, positive health was described as one's ability to adapt and self-manage in the face of social, physical, and emotional challenges.[10] The latter two proposals include difficult-to-measure psychological and social parameters whereas our focus is on measurable medical parameters.

Perhaps the most direct measure of positive health is the years lived without any physical, mental, or social limitation. At the community level, this is measured by the healthy life expectancy. Whether at the individual level or the community level, this can be measured only after death. Biomarkers could be more exact and can be measured when the person is alive. More than a thousand medical parameters can be measured. While the role of most of them is well-documented for causing disease, their physiological role in health protection is mostly obscure. Only few studied their positive features. We extensively searched nearly a thousand publications and reputed websites for the measurable parameters that have a major identifiable protective role in place of their role in causing diseases. For this, an extensive internet search was done for terms such as positive health, health protection, health maintenance, and prevention, with terms such as biomarkers, markers, features, parameters, etc., Documents for individual biomarkers were also studied to locate a relevant document for our review. These include articles, papers, websites, books, and other material. Once identified, the concerned biomarkers may look well-known but a-priori this information is rare.

The biomarkers of positive health would be easy to study when divided into domains and items on the pattern of quality of life (QoL) measurement, although there may be some overlap as in the case of QoL. Each domain has many parameters, but we restrict to a selected set of few parameters that seem major to us on review of the literature so that the assessment of positive health becomes practically feasible. Optimal levels can be proposed later once a consensus is developed on the major parameters of positive health.

Domains and items of positive health

Our review suggests the following five major domains and items have a protective role and could be primarily considered for assessing positive health. They are all interdependent and together contribute to positive health [Figure 1].

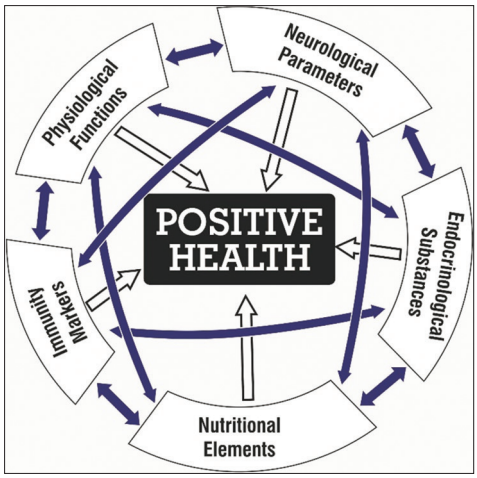

Figure 1: Major domains of positive health and their inter-dependence

Neurological parameters

Neurological parameters perhaps are the most important domain of positive health. These possibly are the most intricate too as they easily transgress to abstracts. However, science is about accepting the challenges and making a beginning that could lead to a clear path.

Our review of the literature suggests that the brain and nervous system parameters that bolster the mechanism to fight the ailments are yet to be investigated. In the absence of exactly measurable parameters, perhaps Montreal Cognitive Assessment Scale[11] can be used to assess brain health at a gross level. P3 amplitude can also be considered as it reflects neural activity related to the attentional and working memory processes.[12]

Studies have demonstrated a negative correlation between gamma-aminobutyric acid (GABA) activity and anxiety.[13] The main physiological effects of GABA include neuronal modulation to improve nervous system disorders, regulation of anxiety, sleeplessness, mood disorders, protection against hypertension, diabetes, nephrotoxicity, and cancer.[14]

Several other parameters are implicated for neural health although they may not be as major. These include growth hormone-releasing hormone with cognition-enhancing effects, nerve growth factor and brain-derived neurotrophic factor as biomarkers of neural health, and Tau protein that maintains functions of nerve cells and structure. Low levels of CRP, IL, and TNF are also implicated in determining cognitive functions and amyloidβ peptides help in preventing cognitive decline in older adults. Prostaglandins regulate brain blood flow and can have a neuroprotective effect by acting on G-protein-coupled receptors. Salivary αamylase, cortisol, secretory immunoglobulin A, and chromogranin A have been investigated as biomarkers of pain and a lower level of norepinephrine indicates lesser anxiety.

In view of the above, among several neurological parameters, the following can be considered major for assessing positive health:

- Montreal Cognitive Assessment Scale
- P3 amplitude
- GABA

Others too are important but possibly not as major.

Endocrinological substances

The endocrine system has a profound effect on the regulation of stress response, growth and development, behavior, immunity, and energy and metabolism. Whereas the implication of hormones in diseases such as thyroidism, Cushing syndrome, and diabetes is evident, these are important for maintaining and protecting health also.

Thyroid hormones help the body to use energy, stay warm, and keep the brain, heart, muscles, and other organs working as they should.[15] They are the key regulators of metabolism and development.[16] Thus, their adequate level is necessary for positive health.

The critical role of insulin in maintaining a healthy level of blood sugar and preventing diabetes is well known.

Estrogen and testosterone have a well-known role in sexual functions as discussed later but they have other protective roles too. Estrogen protects women against heart disease[17] and brain disorders such as Alzheimer's.[18] Systemic estrogen helps protect against bone-thinning disease.[19] The protective role of testosterone is particularly related to pain and inflammation.[20]

Melatonin controls the sleep and wake cycle, which may substantially contribute to positive health. Serotonin is believed to regulate anxiety, happiness, mood, sleep, appetite, memory, and learning ability.[21] and also regulates biological processes including cardiovascular functions, metabolic rate, and temperature control.[22] Oxytocin plays a critical role in social and emotional behavior[23] and can induce antistress-like effects and increase pain threshold.[24] Dopamine is a "feel good" hormone associated with reinforcement and helps in motivation.[25] Thus, these hormones have a vital role in maintaining good health.

Endorphins control the perception of pain and fight stress.[26] They are the body's natural pain killers and mood elevators.[4]

Others that have a role, but probably not as major, are the following. Amino acids stimulate muscle synthesis, and peptides in milk modulate blood pressure, inflammation, and oxidation. Leucine is required for protein synthesis. Hydroxymethylbutyrate enhances and strengthens muscles.

Besides digestion, enzymes are needed to support, maintain, and repair the body and its functions. Amylase and lipase breakdown carbohydrates and pepsin helps in the digestion of proteins – they together play a pivotal role in completing the digestive process.

Amidst so many, the following endocrinological parameters can be considered major candidates for measuring positive health:

- Thyroid hormones
- Insulin
- Estrogen
- Melatonin, serotonin, oxytocin, dopamine
- Endorphins.

Nutritional elements

It is well-known that nutritional elements such as vitamins, folate, trace elements, omega-3 fatty acids, and probiotics, when present in an optimal combination, play a dominant role in maintaining health. But the specific role of various nutrients in preventing and fighting a disease seems still under investigation. Vitamins and minerals play an essential role in a variety of basic metabolic pathways that support fundamental cellular functions, particularly in energy-yielding metabolism, DNA synthesis, oxygen transport, and neuronal functions.[27]

Specifically, vitamin A boosts the immune response in the elderly,[28] vitamin B-complex helps prevent infections and supports or promotes energy level, eyesight, brain functions, digestion, and muscle tone.[29] Vitamin C is an antioxidant that protects from infections and damage to body cells and produces collagen that helps bones and muscles to bond together.[30] It also helps reduce both the physiological and psychological effects of stress.[31] Vitamin D helps regulate the amount of calcium and phosphate – thus keeps bone, teeth, and muscles healthy,[32] and has immunomodulatory effect.[33] Vitamin E has a beneficial effect against oxidative stress.[34] Vitamin K is important for maintaining healthy blood vessels, blood coagulation, bone metabolism, and for regulating blood calcium levels.[35]

Epidemiologic data on the relationship of trace elements with health and disease are incomplete,[36] but it is known that trace elements participate in oxygen-reduction reactions in energy metabolism.[37] Potassium, magnesium, calcium, and other nutrients help in keeping bones together and prevent osteoporosis. Selenium can increase life span and can prevent cancer proliferative. Perhaps the most important is zinc which has a crucial role in multiple biological processes, particularly in regulating immune cell signaling,[38] reducing inflammation, boosting the immune system, reducing the risk of age-related diseases, speeding wound healing, and improving acne.[39] It catalyzes enzyme activity, contributes to protein structure, and regulates gene expression.[40]

Probiotics regenerate the digestive system with good microbes that neutralize the harmful ones. They prevent diarrhea and may boost the immune system. Probiotics can also improve anxiety, depression, autism, and memory[41] and can reduce the severity of certain allergies and eczema.[42]

Omega-3 fatty acids build membranes around each cell in the body, including brain cells, and are associated with increased blood flow in the brain and lower the risk of premature death.[43]

A low level of oxidative stress helps prevent cancer, cardiovascular diseases, neurological diseases, respiratory diseases, rheumatoid arthritis, kidney diseases, and sexual dysfunction.[34] The basic ingredient of oxidative stress is free

radicals, which should be low to prevent gout, rheumatism, renal, calculi, etc.[44] but their presence is needed to synthesize some cellular structures and to be used to fight pathogens.[34] One of the most powerful antioxidants is glutathione that combats free radicals such as malondialdehyde (MDA) and has several other health benefits.

Several other nutritional elements have a protective role although probably not as major. Lactic acid improves the nutritional value of food, controls intestinal infections, improves digestion of lactose, controls some types of cancer, and controls serum cholesterol levels. Glutamine can reduce many kinds of inflammation, fever, joint pain, allergies, and skin irritation. Beta-carotene delays cataract, prevents macular degeneration, and promotes good eye health.

To choose a few, the major protective nutritional elements seem to be:

- Various vitamins (A, B, C, D, E, and K)
- Trace elements, particularly zinc
- Probiotics
- Fatty acids (omega-3, glutamine), lactic acid
- Oxidative stress, particularly glutathione.

Immunity markers

Good immunity is an indisputable asset to fight the microbes and eliminate antigens. Of various immunoglobulins, perhaps IgG and IgM are more important as IgG neutralizes toxins, viruses, and bacteria, and IgM is specialized to activate complement efficiently upon binding antigen.[45] Lymphocytes, which produce antibody molecules and macrophages that kill microorganisms and remove dead cells, are important biomarkers of immunity.

One can go down to neutrophils, dendritic cells, natural killer cells, B and T lymphocytes but we keep them out of our preview so that a practical and easy-to-adopt proposal can be forwarded. Similarly, parameters such as tumor necrosis factor, which plays a critical role in defining intracellular organisms against invasion, are excluded despite their role in enhancing defense mechanisms in the body.

The following items can be considered as the major measurable biomarkers of positive health in the immunity domain:

- IgG and IgM
- Lymphocytes
- Macrophages

Physiological functions

Among many, we restrict to those that are generally considered more important to maintain health and fight diseases. Because of the interdependence, an overlap is imminent.

(i) Markers of Respiratory Functions

Diseases such as lung cancer, respiratory tract infections, pulmonary embolism, asthma, and chronic obstructive pulmonary disease are directly related to the health of the lung. Lung functions such as forced vital capacity (FVC), forced expiratory volume (FEV), and peak expiratory flow rate, can be measured by spirometry. Generally, FEV1/FVC ratio is considered useful to evaluate lung functions.[46] Pulse oximetry estimates the oxygen saturation in the blood that helps replace worn-out cells, supplies energy, and supports the immune system. It also feeds our brain and helps in visual, cognitive, and electroencephalographic function.[47]

The following can be regarded as the major lung function parameters for assessing positive health:

- FEV1/FVC ratio
- Oxygen saturation

(ii) Markers of Reproductive Functions (applicable to reproductive age)

It was observed that the mortality decreased in a dose-response manner as the percentage of motile and morphologically normal spermatozoa and semen volume increased.[48]

Estrogen regulates the menstrual cycle, maintains pregnancy, and aids in sperm production.[49] It protects against cell death and stimulates the birth of new neurons.[50] In men, estradiol is essential for modulating libido, erectile functions, and spermatogenesis.[51] and testosterone triggers puberty and contributes to sex drive, bone mass, fat distribution, muscle mass and strength, and production of red blood cells and sperm.[52] Testosterone is also responsible for regulating sex differentiation, producing male sex characteristics, spermatogenesis, and fertility.[53] High testosterone and low estrogen help in erection in men.[51]

Female reproductive health can be assessed by the levels of follicle-stimulating hormone (FSH), luteinizing hormones (LH), and 17-β estradiol.[54] In women, FSH is responsible for the growth of ovarian follicles that help maintain the menstrual cycle. It may have a direct relation with bone health in women by enhancing bone resorption. LH, in synergy with FSH, stimulates normal follicular growth and ovulation. In men, FSH helps in sperm reproduction. Thus, the major reproductive indicators for positive health could be:

- Males: Semen quality and volume, and testosterone
- Females: FSH, LH, and estradiol.

(iii) Markers of Gastrointestinal Functions (including Liver)

We have not been able to find a measurable indicator that can holistically assess the health of the digestive system.

Besides protecting from liver-specific diseases such as cirrhosis, hepatitis, and liver cancer, adequate liver functions help fight infection and remove toxins from the body's blood. The liver also keeps fluids in the bloodstream from leaking into surrounding tissue and carries hormones, vitamins, and enzymes through the body. Healthy liver slows down aging, increases energy, keeps skin healthy, and helps in hormone balancing.[55]

Although all liver function parameters have importance in maintaining good health, albumin has multiple physiological functions such as maintaining colloidal osmotic pressure,

binding of a wide variety of compounds, and provision of the bulk of plasma antioxidant activity,[56] synthesis of purine/pyrimidine bases, urea and protein synthesis, and gluconcogenesis.[57] Alanine transaminase (ALT) may be a good indicator of overall health, particularly in the context of obesity, metabolic syndrome, and cardiovascular disease.[58]

Among lipids, cholesterol is important for the synthesis of hormones and vitamin D. Specific levels of LDL and HDL cholesterol provide some protection from heart disease. Lipoprotein (a) promotes vascular repair, and the lowest CVD mortality has been observed with a low level of triglycerides.

The major liver functions parameters that can be used as biomarkers of positive health are:

- Albumin, ALT
- Lipid profile

(iv) Markers of Circulatory Functions

Cardiac output determines oxygen delivered to the cells and is an important component of how effectively the heart can meet the body's demands for the maintenance of adequate tissue perfusion. It is related to the left ventricular ejection fraction that assesses global and segmental left ventricular function. We excluded both as these are difficult to measure objectively. However, parameters such as heart rate and blood pressure are completely non-invasive, easy, and amenable to the exact measurement. It is well known that a relatively lower resting heart rate has a protective role against cardiovascular diseases and all-cause mortality, and relatively low blood pressure reduces the risk of heart and kidney diseases.

Among many hematological components, hemoglobin is essential for transferring oxygen in the blood from the lungs to the tissues. Glycosylated Hb (HbA1c) indicates long-term glycemic control. Whereas the adverse effects of high HbA1c are well known, low levels are also suggested to be associated with an increased risk of all-cause mortality.[59] Platelets help the body to control bleeding and they must be present in healthy numbers.

A low hs-CRP level can protect from cardiovascular events. Creatine phosphokinase is important for muscle function, although a high level indicates muscle injury, including possibly the heart. Cardiac troponin regulates contractile function in skeletal and cardiac muscles. There may be several others with protective functions, but the following can be considered as the major circulatory function markers of positive health:

- BP, Heart rate
- Hb and HbA1c level
- Platelet count

(v) Markers of Musculoskeletal Functions

Bone mineral density (BMD) is a common measure of bone strength. A good BMD can save from fractures in the cases of falls or other accidents. The primary task of skeletal muscle is maintaining posture, breathing, and locomotion but it also represents important nutrient storage and metabolic regulator.[60] A low functional aging index based on the sensory and pulmonary parameters, grip strength, and gait speed can indicate positive health.[61]

A healthy body mass index (BMI) indicates good health and long life, is a cornerstone in the prevention of chronic diseases, and is a promotional parameter of healthy aging.[62] It also means more energy, better regulation of body fluids and blood pressure, better sleep, and a reduced risk of several diseases. It naturally implies a reduced burden on the heart and circulation system and a reduced risk of heart disease. Low BMI has been found an independent predictor of pregnancy in women.[63] Healthy BMI also raises life satisfaction.[64]

Thus, the major musculoskeletal parameters that can be considered as candidates for assessing positive health are:

- BMD
- Functional aging index, including handgrip strength
- BMI

(vi) Markers of Urinary Functions

Good kidney functions help in regulating blood pressure, the make-up of the blood, maintain hormones, and producing hormones for bones to make more blood cells. They metabolize vitamin D and maintain a proper balance between water, electrolytes, acids, and bases. They release the hormone that directs production of RBC and keeps blood minerals in balance.

Glomerular filtration rate (GFR) is considered the optimal way to measure kidney function.[65] There is evidence that creatine might prevent skin aging, helps muscles gain strength, and may help minimize neurogenerative disorders[66] but important for the health of the kidney is a relatively low creatinine level in serum. A good indicator of health is a low level of protein-creatinine ratio because its level is associated with all-cause mortality.[67]

A balanced pH keeps our systems operating the way they should.[68] Human life requires a tightly controlled pH level to survive.[69]

Thus, the major kidney parameters that can indicate positive health are:

- GFR
- Protein/creatinine ratio
- pH value

Discussion

The notion of positive health provides a context for methodological and theoretical debate that can enrich the theory and practice of health assessment.[70] For Harrison *et al*.,[71] the concept of positive health included harmonious family balance and mental and emotional stability. An editorial in the Lancet explained health as the ability to adapt.[72] Previous endeavors[9,10] are predominantly based on psychological and social factors such as positive emotions, life satisfaction, and happiness. These indeed could be important

determinants, but they are subjective and difficult to measure. Evidence suggests that such factors mostly culminate in physiological changes such as better immunity levels and more balanced hormonal levels that can be exactly measured. This communication targets such biomarkers. The information regarding the protective role of these factors is mostly lacking and we dug the literature to identify the major protective parameters. Their link to positive health outcomes can help design interventions to build and sustain these assets and help people to increase their chance of living healthier and longer life.[73] To achieve parsimony and feasibility, we have restricted to a few biomarkers that seemed major to us. Although no medical parameter is absolute, our review suggests that endorphins, semen quality in men, FEV1/FVC ratio, oxygen saturation, BMD, P3 amplitude, and handgrip strength are examples of parameters whose higher levels generally indicate increasingly positive health. Measurement of most of these are cost-effective and the remaining will become cheaper when the idea of positive health catches up and used on a large scale.

Among thousands of medical parameters, the initial identification of nearly 50 major biomarkers of positive health in this communication shows that it is feasible to objectively assess positive health. Once a consensus is developed on the relevant parameters, an exercise can be undertaken to identify the optimal levels of the parameters that signify positive health.

Our effort may be ahead of time because many of the body's defense mechanisms are not properly understood yet. The link between physiological processes and positive outcomes seems to have not been fully investigated. We believe it is time to think of approaches that can contribute to our understanding of how body functions work to defend from ailments and fill up this epistemic uncertainty. Our proposal may initiate a discussion on biomarkers of positive health and characterize the parameters for intervention that could increase the healthy life. This may also help in identifying the data gaps that require attention in this context.

Limitations

We have been quite brief since the endeavor here is just to propose an idea and show that it is useful and feasible although we agree that much work is required to make it operational in the actual setup. The references are quoted only for the major biomarkers but the source of all the statements is available from the corresponding author.

The domains and items included in this article may give the impression that psychological and spiritual aspects have been ignored but we believe that most of these also ultimately affect biomarkers such as hormones. Nonetheless, those psychological and spiritual aspects have been excluded from our framework that do not affect biomarkers.

Conclusion

A novel proposal to assess the positive health of individuals has been developed with five domains and nearly 50 items. Despite being preliminary, this communication possibly covers most major measurable biomarkers and could be adequate to proceed ahead with operationalizing the concept of positive health and its assessment. The framework may also help in identifying the data gaps that can be used to develop policies for improving the health of the people.

Contribution of the authors

AI proposed the idea, developed it, and prepared the draft. GC helped in expanding the idea, searching the literature, and contributing to the manuscript. SV and SS searched the literature and proposed changes. AT provided inputs for improvement in the medical content of the manuscript. All the authors reviewed the draft and approved it.

Highlights

- The concept of positive health as the capability to counter ailments before their onset and to live a long healthy life has so far mainly concentrated on lifestyle factors. This article identifies objectively measurable major biomarkers of positive health that can help operationalize this concept at the individual level.

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Conflicts of interest

There are no conflicts of interest.

References

1. Wojcik O, Miller Mshp CE, Plough AL. Aligning health and social systems to promote population health, well-being, and equity. Am J Public Health 2020;110(S2):S176-7.
2. Indrayan A, Vishwakarma G, Sarmukaddam S, Verma S. Beyond "Normal": Optimal levels of medical parameters for assessing positive health. Am J Int Med 2021;9:166-70.
3. Harden KP, Klump KL. Introduction to the special issue on gene-hormone interplay. Behav Genet 2015;45:263-7.
4. Harvard Health. Endorphins: The Brain's Natural Pain Reliever. July 20, 2021. Available from: https://www.health.harvard.edu/mind-and-mood/endorphins-the-brains-natural-pain-reliever.
5. Childs CE, Calder PC, Miles EA. Diet and immune function. Nutrients 2019;11:1933.
6. Schwimmer H, Stauss HM, Abboud F, Nishino S, Mignot E, Zeitzer JM. Effects of sleep on the cardiovascular and thermoregulatory systems: A possible role for hypocretins. J Appl Physiol (1985) 2010;109:1053-63.
7. Anonymous. Why positive health? Cal State J Med 1924;22:28.
8. Indrayan A, Sarmukaddam S. Medical Biostatistics. 1st ed. New York: Marcel Dekker; 2001. *P* 164.
9. Seligman MEP. Positive health. Applied Psychol Int Rev 2008;57:3–18.
10. Huber M, Knottnerus JA, Green L, van der Horst H, Jadad AR, Kromhout D, *et al*. How should we define health? BMJ 2011;343:d4163.
11. MoCA. Cognitive Assessment. https://www.mocatest.org/-. [Last accessed on 2021 Dec 18].
12. Polich J, Kok A. Cognitive and biological determinants of P300: An integrative review. Biol Psychol 1995;41:103-46.
13. Krishnakumar D, Hamblin MR, Lakshmanan S. Meditation and yoga can modulate brain mechanisms that affect behavior and anxiety: A modern scientific perspective. Anc Sci 2015;2:13-9.
14. Grewal J. Gamma-Aminobutyric Acid (GABA): A versatile bioactive compound. Eur J Molecular Clin Med 2020;7:3068-75.
15. American Thyroid Association. Thyroid Function Tests. Available from: https://www.thyroid.org/thyroid-function-tests/-. [Last accessed on 2021 Dec 18].

16. Boelaert K, Franklyn JA. Thyroid hormone in health and disease. J Endocrinol 2005;187:1-15.
17. Paranjape SG, Turankar AV, Wakode SL, Dakhale GN. Estrogen protection against coronary heart disease: Are the relevant effects of estrogen mediated through its effects on uterus--such as the induction of menstruation, increased bleeding, and the facilitation of pregnancy? Med Hypotheses 2005;65:725-7.
18. Simpkins JW, Perez E, Wang X, Yang S, Wen Y, Singh M. The potential for estrogens in preventing Alzheimer's disease and vascular dementia. Ther Adv Neurol Disord 2009;2:31-49.
19. Gambacciani M, Levancini M. Hormone replacement therapy and the prevention of postmenopausal osteoporosis. Prz Menopauzalny 2014;13:213-20.
20. Vodo S, Bechi N, Petroni A, Muscoli C, Aloisi AM. Testosterone-induced effects on lipids and inflammation. Mediators Inflamm 2013;2013:183041.
21. Dfarhud D, Malmir M, Khanahmadi M. Happiness and health: The biological factors – systematic review article. Iran J Public Health 2014;43:1468-77.
22. Berger M, Gray JA, Roth BL. The expanded biology of serotonin. Annu Rev Med 2009;60:355-66.
23. Olff M, Frijling JL, Kubzansky LD, Bradley B, Ellenbogen MA, Cardoso C, *et al*. The role of oxytocin in social bonding, stress regulation and mental health: An update on the moderating effects of context and interindividual differences. Psychoneuroendocrinology 2013;38:1883-94.
24. Uvnas-Moberg K, Petersson M. Oxytocin, einVermittler von Antistress, Wohlbefinden, sozialer Interaktion, Wachstum und Heilung [Oxytocin, a mediator of anti-stress, well-being, social interaction, growth and healing]. Z Psychosom Med Psychother 2005;51:57-80. German.
25. Bromberg-Martin ES, Matsumoto M, Hikosaka O. Dopamine in motivational control: Rewarding, aversive, and alerting. Neuron 2010;68:815-34.
26. Sprouse-Blum AS, Smith G, Sugai D, Parsa FD. Understanding endorphins and their importance in pain management. Hawaii Med J 2010;69:70-1.
27. Tardy AL, Pouteau E, Marquez D, Yilmaz C, Scholey A. Vitamins and minerals for energy, fatigue and cognition: A narrative review of the biochemical and clinical evidence. Nutrients 2020;12:228.
28. Rumore MM. Vitamin A as an immunomodulating agent. Clin Pharm 1993;12:506-14.
29. Healthline. Why Is Vitamin B Complex Important, and Where Do I Get It? Available from: https://www.healthline.com/health/food-nutrition/vitamin-b-complex-. [Last accessed on 2021 Nov 15].
30. DePhillipo NN, Aman ZS, Kennedy MI, Begley JP, Moatshe G, LaPrade RF. Efficacy of vitamin C supplementation on collagen synthesis and oxidative stress after musculoskeletal injuries: A systematic review. Orthop J Sports Med 2018;6:2325967118804544.
31. Staff P. "Vitamin C: Stress buster-Psychology Today". 2003. Available from: https://www.psychologytoday.com/intl/articles/200304/vitamin-c-stress-buster-. [Last accessed on 2021 Oct 11].
32. NHS. 2019. "Vitamin D." Available from: https://www.nhs.uk/conditions/vitamins-and-minerals/vitamin-d/-. [Last accessed on 2021 Oct 11].
33. Sassi F, Tamone C, D'Amelio P. Vitamin D: Nutrient, hormone, and immunomodulator. Nutrients 2018;10:1656.
34. Pizzino G, Irrera N, Cucinotta M, Pallio G, Mannino F, Arcoraci V, *et al*. Oxidative stress: Harms and benefits for human health. Oxid Med Cell Longev 2017;2017:8416763.
35. Gröber U, Reichrath J, Holick MF, Kisters K. Vitamin K: An old vitamin in a new perspective. Dermatoendocrinol 2015;6:e968490.
36. National Research Council (US) Committee on Diet and Health. Diet and Health: Implications for Reducing Chronic Disease Risk. Washington (DC): National Academies Press (US); 1989. Available from: https://pubmed.ncbi.nlm.nih.gov/25032333/.
37. Chojnacka K, Saeid A, editors. Recent Advances in Trace Elements. Wiley-Blackwell; 2018. Available from: https://www.wiley.com/en-au/Recent+Advances+in+Trace+Elements-p-9781119133803.
38. Kim B, Lee WW. Regulatory role of zinc in immune cell signaling. Mol Cells 2021;44:335-41.
39. Kubala J. Zinc: Everything You Need to Know: Healthline. November 14, 2018. Available from: https://www.healthline.com/nutrition/zinc-. [Last accessed on 2021 Nov 18].
40. Trumbo P, Yates Aa, Schlicker S, Poos M. Dietary references intakes. J Acad Nutri Dietetics 2001;101:294-301.
41. Wang H, Lee IS, Braun C, Enck P. Effect of probiotics on central nervous system functions in animals and humans: A systematic review. J Neurogastroenterol Motil 2016;22:589-605.
42. Makrgeorgou A, Leonardi-Bee J, Bath-Hextall FJ, Murrell DF, Tang ML, Roberts A, *et al*. Probiotics for treating eczema. Cochrane Database Syst Rev 2018;11:CD006135.
43. Harris WS, Tintle NL, Imamura F, Qian F, Korat AVA, Marklund M, *et al*. Blood n-3 fatty acid levels and total and cause-specific mortality from 17 prospective studies. Nat Commun 2021;12:2329.
44. Pham-Huy LA, He H, Pham-Huy C. Free radicals, antioxidants in disease and health. Int J Biomed Sci 2008;4:89-96.
45. Janeway CA Jr, Travers P, Walport M, Shlomchik MJ. Immunobiology: The Immune System in Health and Disease. 5th ed. New York: Garland Science; 2001. Available from: https://www.ncbi.nlm.nih.gov/books/NBK10757/.
46. Torén K, Schiöler L, Lindberg A, Andersson A, Behndig AF, Bergström G, *et al*. The ratio FEV_1/FVC and its association to respiratory symptoms-A Swedish general population study. Clin Physiol Funct Imaging 2021;41:181-91.
47. Hafen BB, Sharma S. Oxygen Saturation. 2021 Aug 12. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2021 Jan–. Available from: https://pubmed.ncbi.nlm.nih.gov/30247849/.
48. Jensen TK, Jacobsen R, Christensen K, Nielsen NC, Bostofte E. Good semen quality and life expectancy: A cohort study of 43,277 men. Am J Epidemiol 2009;170:559-65.
49. Dostalova P, Zatecka E, Dvorakova-Hortova K. Of oestrogens and sperm: A review of the roles of oestrogens and oestrogen receptors in male reproduction. Int J Mol Sci 2017;18:904.
50. Wise PM, Suzuki S, Brown CM. Estradiol: A hormone with diverse and contradictory neuroprotective actions. Dialogues Clin Neurosci 2009;11:297-303.
51. Schulster M, Bernie AM, Ramasamy R. The role of estradiol in male reproductive function. Asian J Androl 2016;18:435-40.
52. Wein. Understanding How Testosterone Affects Men. NIH. 23 September, 2013. Available from: https://www.nih.gov/news-events/nih-research-matters/understanding-how-testosterone-affects-men-. [Last accessed on 2021 Nov 08].
53. Nassar G, Leslie S. Physiology**:** Testosterone**.** Treasure Island (FL): Stat Pearls Publishing; Sept 26, 2018. Available from: https://europepmc.org/article/NBK/nbk526128.
54. Navot D, Rosenwaks Z, Margalioth EJ. Prognostic assessment of female fecundity. Lancet 1987;2:645-7.
55. Foreman D. Why Liver Health is so Important? Algatech. July 7, 2019. Available from: https://www.algatech.com/why-liver-health-is-so-important/-. [Last accessed on 2021 Dec 03].
56. Levitt DG, Levitt MD. Human serum albumin homeostasis: A new look at the roles of synthesis, catabolism, renal and gastrointestinal excretion, and the clinical value of serum albumin measurements. Int J Gen Med 2016;9:229-55.
57. Ndrepepa G. Aspartate aminotransferase and cardiovascular disease—A narrative review. J Lab Prec Med 2020;6. doi: 10.21037/jlpm-20-93.
58. Kim W. Serum activity of alanine aminotransferase (ALT) as an indicator of health and disease. Hepatology 2008;47:1363-70.
59. Carson AP, Fox CS, McGuire DK, Levitan EB, Laclaustra M, Mann DM, *et al*. Low hemoglobin A1c and risk of all-cause mortality among US adults without diabetes. Circ Cardiovasc Qual Outcomes 2010;3:661-7.
60. Wolfe RR. The underappreciated role of muscle: Am J ClinNutr 2006;84:475-82.
61. Finkel D, Sternäng O, Jylhävä J, Bai G, Pedersen NL. Functional aging index complements frailty in prediction of entry into care and mortality. J Gerontol A Biol Sci Med Sci 2019;74:1980-6.
62. Fontana L, Hu FB. Optimal body weight for health and longevity: Bridging basic, clinical, and population research. Aging Cell 2014;13:391-400.
63. Bond RT, Nachef A, Adam C, Couturier M, Kadoch IJ, Lapensée L,

et al. Obesity and infertility: A metabolic assessment strategy to improve pregnancy rate. J Reprod Infertil 2020;21:34-41.
64. Habibov N, Auchynnikava A, Luo R, Fan L. A healthy weight improves life satisfaction. Int J Health Plann Manage 2019;34:396-413.
65. Cimmino CJ. Benefits of direct glomerular filtration rate (GFR) determination versus creatinine-based tests for evaluating renal function. J Am Osteopath Assoc 1998;98:437-44.
66. Riesberg LA, Weed SA, McDonald TL, Eckerson JM, Drescher KM. Beyond muscles: The untapped potential of creatine. Int Immunopharmacol 2016;37:31-42.
67. Fulks M, Stout RL, Dolan VF. Urine protein/creatinine ratio as a mortality risk predictor in non-diabetics with normal renal function. J Insur Med 2012;43:76-83.
68. Waugh A, Grant A, editors. Anatomy and Physiology in Health and Illness. 10th ed. London: Churchill Livingstone Elsevier; 2007.
69. Schwalfenberg GK. The alkaline diet: Is there evidence that an alkaline pH diet benefits health? J Environ Public Health 2012;2012:727630.
70. Locker D, Gibson B. The concept of positive health: A review and commentary on its application in oral health research. Community Dent Oral Epidemiol 2006:34:161-73.
71. Harrison GG, Kagawa-Singer M, Foerster SB, Lee H, Pham Kim L, Nguyen TU, *et al*. Seizing the moment: California's opportunity to prevent nutrition-related health disparities in low-income Asian American population. Cancer 2005;104 (12 Suppl):2962-8.
72. Editorial. What is health? The ability to adapt. Lancet 2009;373:781.
73. Positive Health. "What is positive health?". Available from: https://positivehealthresearch.org/. [Last accessed on 2021 Dec 11].