

RESEARCH ARTICLE

Systematic review and meta-analysis shows a specific micronutrient profile in people with Down Syndrome: Lower blood calcium, selenium and zinc, higher red blood cell copper and zinc, and higher salivary calcium and sodium

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Abstract

Different metabolic profiles as well as comorbidities are common in people with Down Syndrome (DS). Therefore it is relevant to know whether micronutrient levels in people with DS are also different. This systematic review was designed to review the literature on micronutrient levels in people with DS compared to age and sex-matched controls without DS. We identified sixty nine studies from January 1967 to April 2016 through main electronic medical databases PubMed, Scopus, and Web of knowledge. We carried out meta-analysis of the data on four essential trace elements (Cu, Fe, Se, and Zn), six minerals (Ca, Cl, K, Mg, Na, and P), and five vitamins (vitamin A, B9, B12, D, and E). People with DS showed lower blood levels of Ca (standard mean difference (SMD) = -0.63; 95% confidence interval (CI): -1.16 to -0.09), Se (SMD = -0.99; 95% CI: -1.55 to -0.43), and Zn (SMD = -1.30; 95% CI: -1.75 to -0.84), while red cell levels of Zn (SMD = 1.88; 95% CI: 0.48 to 3.28) and Cu (SMD = 2.77; 95% CI: 1.96 to 3.57) were higher. They had also higher salivary levels of Ca (SMD = 0.85; 95% CI: 0.38 to 1.33) and Na (SMD = 1.04; 95% CI: 0.39 to 1.69). Our findings that micronutrient levels are different in people with DS raise the question whether these differences are related to the different metabolic profiles, the common comorbidities or merely reflect DS.

Introduction

Down Syndrome (DS) or trisomy 21 is a congenital condition characterized by phenotypic features as well decreased growth and development. The major maternal risk factors are advanced age [1] and impaired folate-homocysteine metabolism [2]. Pregnant women can be screened if they carry a fetus with DS [3]. If these results are out of line, doctors can confirm prenatal diagnosis [4, 5]. Globally, most confirmed pregnancies are terminated; average DS pregnancy termination rates are 67% and 85% [6]. Nevertheless, DS remains the most common recognized genetic cause of mental retardation and is reported to affect approximately 1 in 732 live born American infants ($\sim 0.14\%$) [7]. Similar levels are found in the Netherlands (between 0.14 and 0.15%) [8]. Because of a growing trend in advanced maternal age, the frequency of DS has more than doubled over recent decades [9]. Moreover, the prevalence of this lifetime condition is increasing as the life-expectancy of people with DS has increased to 60 years [10].

DS is associated with various life-limiting or life-threatening comorbidities. Congenital heart disease is the most common cause of death at adulthood, pneumonia and other respiratory infections at both childhood and senescence [9]. In addition, people with DS frequently suffer from other complications affecting their quality of life (QoL). They suffer from different degrees of cognitive impairment that may hamper their memory function [11] and neurodevelopmental disorders, such as autism spectrum disorders. Early-onset neurological diseases like dementia and seizure, are relatively common [12, 13]. Resting metabolic rate is reduced in people with DS, making them more prone to develop metabolic disorders, as overweight, obesity, and diabetes [14–16]. Immune-mediated disorders such as celiac disease and thyroid disorders (hypo- or hyperthyroidism, and autoimmune thyroiditis), also affect people with DS more frequently [17]. Due to the high rates of comorbidity, specific clinical guidelines are developed to manage health and quality of life of people with DS (4).

Besides these clinical condition, several metabolic profiles are different in people with DS: the amino acid profile (low serotonin [18, 19] and serine [20], high lysine [21] and cysteine [20] in blood), low gamma-Aminobutyric acid and glutamate levels in the central nervous system [22]. Also, hormonal changes occur, most notably thyroid dysfunction (low T-4 and high TSH) and gonadal dysfunction (high FSH and LH) [23, 24]. Despite these observations, clinical studies have not provided evidence that normalization of amino acid or thyroid hormone profile improves health, growth, or QoL [23, 25].

Micronutrients perform complex metabolic functions to preserve metabolic balance [26]: Fe and the trace elements Zn, Cu and Se act as coenzymes, while vitamins A, C and E, act as free radical scavengers. Their deficiency or overload may contribute to cell injury. Since high prevalence of comorbidities and differences in metabolic profiles exist, we undertake the current study to evaluate whether micronutrient levels in people with DS are different. Therefore we conduct a systematic review and meta-analysis study on the micronutrient status in people with DS.

Materials and methods

We use the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement [27] to improve the present systematic review and meta-analysis (S1 PRISMA Checklist and S1 Fig). Prior the authors (AS and NR) developed the study protocol which is available on request.

Literature search and meta-analysis

We conducted the present systematic review and meta-analysis to recognize all studies measuring concentrations of five trace elements (Cu, Fe, Mn, Se, and Zn), six minerals (Ca, Cl, K,

Mg, Na, and P), and six vitamins (vitamins A, B9, B12, C, D, and E) in whole blood, red cells, plasma, serum, hair or saliva among people with DS and simultaneously in age, sex, and race matched healthy controls. We identified relevant studies from January 1967 to April 2016 by searching electronic medical databases, PubMed, Scopus, and Web of knowledge (S1 Text). To find additional studies, we also checked reference lists of all relevant articles.

Original articles were included if they met both criteria; 1) they did measure levels of micronutrients in the samples we study (whole blood, plasma, serum, red cells, hair and saliva) in people with DS and healthy controls, and 2) provided results, including the total number of subjects and controls with mean and standard deviation (SD). We also included studies providing sufficient data (such as median, first quartile, and third quartile, or median and range, or median and standard error) to calculate mean and SD. We excluded studies that measured protein or mRNA expression of micronutrients in tissues or samples other than red cells.

We extracted from each included publication; first-named author, year of publication, location of study, the assay that was used for micronutrient measurement, type of specimen taken from subjects, number of subjects and controls, demographic characteristics, mean \pm SD of the micronutrient levels and the used scale of micronutrient levels.

We performed all of the statistical analyses using Review Manager Version (Version 5.3. Copenhagen: The Nordic Cochrane Centre, the Cochrane Collaboration, 2014). As explained elsewhere [28], we created the continuous type of outcome and entered the number of participants in subject and control groups and the mean and SD of the micronutrient levels. Fixed effects and random effects were interchangeably used as the analysis model. Heterogeneity was determined using Q statistic tests and the I^2 index. According to the Cochrane guidelines, an I^2 less than 40% would mean that the inconsistency across studies is not important. In this case, we planned to use the fixed effects model. If the I^2 estimates fluctuated more than 40% we intended to use the random effects procedure as the analysis model. As well, the standardized mean difference (SMD) and mean difference (MD) were interchangeably used for measurement of effect. The SMD was applied if studies used different measurement scales or assays. Otherwise we used the MD for measurement of effect. Publication bias was assessed when there were five or more than five studies using the degree of funnel plot asymmetry. A *P* value less than 0.05 was considered significant.

Study selection and data extraction

As recommended by the PRISMA guidelines and graphically illustrated in Fig 1, the study selection is a procedure composed of four main steps: identification, screening, eligibility, and inclusion. The “identification” step aimed at acquisition of all the relevant papers is a process including forward and backward searches and then removal of duplicate records. The “screening” step is to screen results based on title and/or abstract. The apparently relevant papers are examined by the authors for “eligibility”. The final step is to include articles that met eligible criteria in systematic review and in meta-analysis if applicable. The initial search resulted in 4,656 records (Fig 1). After removing duplicate publications ($n = 1,450$) and excluding reviews, letters, editorials, or book chapters ($n = 701$), 2,505 discrete manuscripts were identified for review. Of these, 2,388 publications were excluded based on title and/or abstract. We reviewed the remaining 117 publications. Based on detail review, we excluded 40 additional publications: eight articles were excluded because they did not report adequate data [29–36] another eight because a healthy control group lacked [37–44]. One was a duplicate record [45]. Some abstracts or titles were likely to be related, but the full texts were not available to obtain sufficient data for analysis or to ensure they were relevant [46–76]. Eventually, sixty nine studies were included [77–145]. Meta-analysis was performed when there were three or more

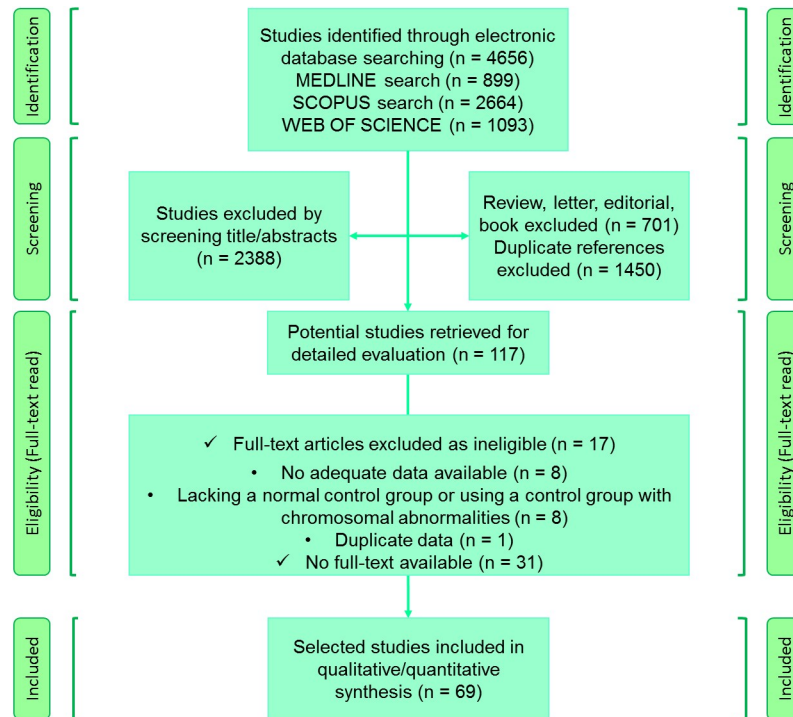


Fig 1. Search results and study selection.

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comparisons regarding the title. Thus we could not carry out quantitative synthesis when there were less than three comparisons. Characteristics of included studies are summarized in [S1](#), [S2](#) and [S3](#) Tables.

Quality assessment

We appraised the quality of included studies using the Newcastle–Ottawa Scale (NOS) designed for observational studies [146]. The NOS is composed for the assessment of three main aspects of observational studies; sample selection, comparability of cases and controls, and exposure. Using this scale, possible scores range from 0 to 9. Studies with scores of 7–9 stars have the lowest risk of bias and represent the highest quality, whereas studies with scores less than 4 stars have the highest risk of bias and the lowest quality. Studies with scores of 4–6 stars have the moderate risk of bias and quality.

Results

More than thirty meta-analyses were performed and the [S4 Table](#) provides an overview of all these meta-analyses and relevant findings. Here, due to limitations of space, the results of meta-analyses associated with significant p value are expressed in [Table 1](#). Significant results were obtained for the trace elements Cu, Se and Zn and for the minerals Ca and Na too (Figs 2–14). However the most striking results were related to the trace element Zn. Thirty one studies were retrieved on Zn measurements [77–107]. They were published between 1970 and 2014 and all but four conducted in Europe [81–88, 90–98, 102] or America. The largest analysis was performed on thirty comparisons including 1,562 participants and indicated lower blood levels of Zn in people with DS than in control subjects. Also plasma, serum, and red blood cell Zn values were lower. But hair Zn levels were higher in people with DS. Similarly, a

Table 1. Summary of meta-analyses associated with the significant p value.

Outcome	Comparisons (n)	Cases (n) Controls (n)	Heterogeneity χ^2 p value	Inconsistency I^2 %	Effect measure SMD 95% CI	Overall effect Z p value
Blood Zn	30	794/768	405.87 (< .00001)	93	-1.30 [-1.75, -0.84]	5.59 (< .00001)
Plasma Zn	17	343/356	234.06 (0.0005)	93	-1.23 [-1.93, -0.54]	3.47 (0.0005)
Serum Zn	13	451/412	107.29 (< .00001)	89	-1.44 [-1.93, -0.95]	5.75 (< .00001)
RBC Zn	6	95/123	69.70 (< .00001)	93	1.88 [0.48, 3.28]	2.63 (0.009)
RBC Zn	4	78/95	15.95 (0.001)	81	2.62 [1.59, 3.66]	4.97 (< .00001)
Hair Zn	3	155/97	4.58 (0.1)	56	-0.54 [-0.97, -0.12]	2.50 (0.01)
RBC Cu	5	83/125	13.88 (0.008)	71	2.77 [1.96, 3.57]	6.74 (< .00001)
Blood Se	16	287/517	162.31 (< .00001)	91	-0.99 [-1.55, -0.43]	3.44 (0.0006)
Serum Se	4	108/115	5.35 (0.15)	44	-0.60 [-0.97, -0.23]	3.21 (0.001)
Whole blood Se	3	32/124	3.22 (0.20)	38	-2.60 [-3.32, -1.89]	7.11 (< .00001)
Blood Ca	4	98/154	9.92 (0.02)	70	-0.63 [-1.16, -0.09]	2.28 (0.02)
Saliva Ca	8	274/243	104.04 (< .00001)	93	0.85 [0.38, 1.33]	3.53 (0.0004)
Saliva Na	8	203/173	56.99 (< .00001)	88	1.04 [0.39, 1.69]	3.14 (0.002)

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meta-analysis of sixteen comparisons involving 804 participants revealed lower blood Se concentrations in people with DS. Additionally, blood Ca was decreased. But salivary levels of Ca and Na were increased (Table 1).

Discussion

The present systematic review was designed to review current literature on micronutrient levels in people with DS compared with controls. We identified sixty nine studies by electronic medical databases up to April 2016. Meta-analysis was performed if there were three or more comparisons regarding the title. Accordingly we were able to carry out meta-analysis of data regarding four trace elements (Cu, Fe, Se, and Zn), six minerals (Ca, Cl, K, Mg, Na, and P), and four vitamins (vitamin A, B9, B12, D, and E). As noted in Table 1, people with DS had lower blood levels for Zn, Se, and Ca and higher red blood cell levels for Cu and Zn (Figs 2–14). Also, lower hair levels of Zn and higher salivary levels of Ca and Na were found. No

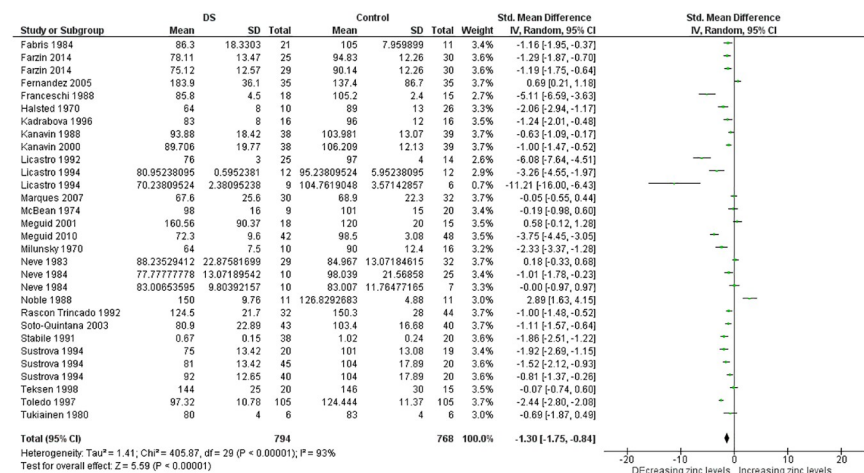


Fig 2. Meta-analysis of blood levels of zinc.

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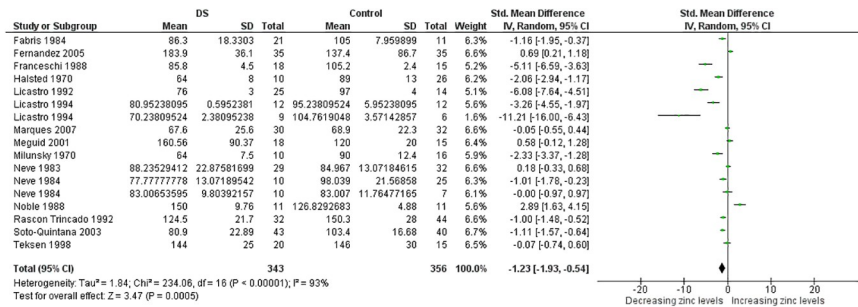


Fig 3. Meta-analysis of plasma levels of zinc.

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differences were found between cases and controls with regard to Cl, Fe, K, Mg, P, and vitamin levels.

We found evidence that micronutrient status is different in people with DS for the trace elements Cu, Se, and Zn and also for the minerals Ca and Na. Amino acid abnormalities and high parathyroid hormone (PTH) levels may be implicated in micronutrient changes in people with DS. The important consequences (including thyroid dysfunction, immune disorders, and growth abnormalities) that will follow from this condition are among the most common comorbidities in people with DS.

Causes

Amino acid abnormalities. Analysis of amniotic fluid indicated elevations in essential amino acid levels in the DS group compared to the healthy group. This might reflect profound amino acid deficiency in fetuses with DS as demonstrated in cortical tissues [147]. Deficiency of essential amino acid persists in the elderly people with DS [148]. Therefore, people with DS display altered amino acid profile from gestation throughout lifetime. Abnormal amino acid metabolism might predispose individuals to serious health problems, importantly brain and behavior disorders. This might explain why dementia occurs more frequently and earlier in people with DS [149]. Additionally amino acids and their binding to trace elements (notably Zn) help maintain proper trace elements levels [150, 151]. Histidine is among amino acids which particularly contribute to the formation of amino acid-metal complex. Studies have shown reduction in histidine levels in brain tissues of people with DS [152]. Thus, amino acid abnormalities might increase urinary excretion of Zn and thereby causing Zn deficiency in people with DS. On the other side, since the trace element Se takes part in the formation of some amino acids [153], its deficiency might in turn exacerbate amino acid abnormalities

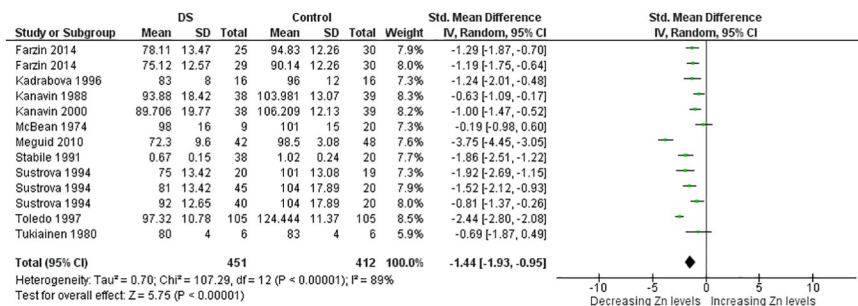


Fig 4. Meta-analysis of serum levels of zinc.

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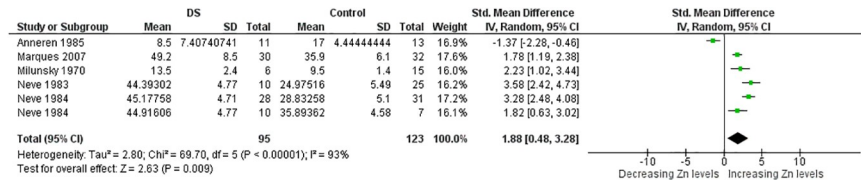


Fig 5. Meta-analysis of intra-erythrocyte levels of zinc.

<https://doi.org/10.1371/journal.pone.0175437.g005>

related to the DS and relevant sequelae, for example Zn deficiency. While the uptake of metals in red blood cells appears to be increased as Zn and Cu levels on red blood cells were elevated. Elevation in these metals implies increased activity of CuZn superoxide dismutase enzyme in red blood cells from people with DS [154].

Parathyroid hormone (PTH). It is able to inhibit proximal reabsorption of ions such as Ca and Na [155] and as well to induce salivary secretion of these electrolytes [156]. Therefore elevated salivary levels of Ca and Na might reflect high PTH levels which have been found in individuals with DS [142]. Additionally, high salivary calcium concentrations are suggested as an indicator of osteoporosis [157] and orthopedic problems and low bone mineral density (BMD) are among the most frequently encountered problems in people with DS [158]. Therefore high salivary calcium levels might represent low calcium concentrations in the extracellular fluid, leading to increase in PTH levels and thereby reducing BMD in people with DS. As expected, Ca supplementation could be effective in reducing PTH concentrations and in improving bone turnover in people with DS [159].

Other. There are other physiological characteristics related to the DS that may cause trace element changes. Of note, many proteins [160] take part in Zn homeostasis [161] and therefore any changes related to these proteins are reflected by altered Zn concentrations. Particularly metallothioneins which are low molecular weight metal-binding proteins have affinity to specific metals (favourably Cu and Zn) and thereby affecting absorption, distribution, and metabolism of these metals [162].

Animal model of DS showed that higher levels of metallothionein 3 in trisomic astrocytes [163] might justify lower free Zn concentrations. The Cu transport is mediated by carriers, importantly the Cu transporter (Ctr) 1. Intestinal malabsorption of Cu induced by deficiency of the Ctr1 gene in murine intestinal cells resulted in tissue copper accumulation [164]. It has to be investigated if intestinal absorption of Cu in people with DS is impaired. Meanwhile the concentrations of superoxide dismutase (SOD1) are elevated in red cells from people with DS [144]. High Cu and SOD1 levels in red cells might lead to oxidative stress and cell degeneration [165]. Because even regular exercise was not helpful in reducing SOD1 levels [166], it seems that effort must be shifted towards preventing Cu/Zn accumulation in red cells. However, regarding Se, the dietary intake is suggested as the best determinant of Se status and Se, with a few exceptions (e.g. parenteral nutrition and the acquired immunodeficiency syndrome), is well-absorbed [167]. Therefore low Se levels in people with DS seem to be the result of

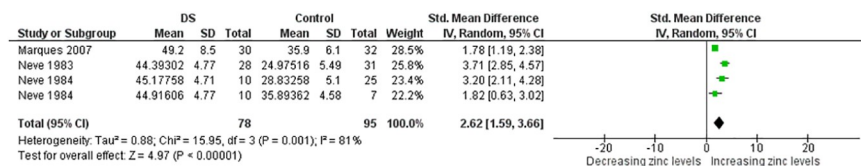


Fig 6. Meta-analysis of intra-erythrocyte levels of zinc.

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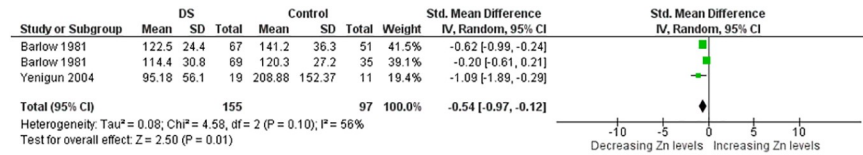


Fig 7. Meta-analysis of hair levels of zinc.

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inadequate intake. Altogether, at the moment, health professionals must consider assessment of micronutrients (especially Zn) in management of comorbidities and in prevention of potential complications people with DS may develop. When prescribing nutritional supplements, physicians should be aware of all the drugs the patient is taking and be vigilant for the occurrence of toxic effects as well [168, 169].

Consequences

Thyroid dysfunction. People with DS are a vulnerable group to thyroid disorders [170]. Thyroid dysfunction may be a cause of lower intellectual function [171] and lower basal metabolic rate [172]. It is, thus, of importance to identify the causes responsible for this condition. Deficiency of either the trace element Zn [172, 173] or Se [173, 174] can cause impairment in thyroid hormone metabolism. Zn supplementation has proved to be promising in improvement of thyroid function in people with DS and low Zn levels [175, 176]. With regards to Se supplementation, the effect was modest in the general population [177]. It has not been assessed yet whether Se therapy can improve thyroid function in people with DS or not.

Immune disorders. Immunodeficiency, infectious diseases, and autoimmune disorders are frequently observed among people with DS [178] to the extent that the DS is expressed as a model of immunodeficiency [179]. Persistent Zn deficiency can lead to inflammation, exacerbating clinical status of patients who suffer from inflammatory and autoimmune diseases [180]. While Se deficiency has been frequently linked with development and exacerbation of viral infections and related complications, e.g. cardiomyopathy [181, 182].

Growth abnormalities and orthopedic issues. Ca plays a crucial role in bone growth and in muscle mineralization and its deficiency may cause osteoporosis or osteomalacia [183]. In addition Zn is involved in osteogenic activity and its deficiency might cause or aggravate growth abnormalities in people with DS [184].

Possible effects of ages and gender

Among studies included in the present meta-analysis, few studies have examined the effect of age [78, 82–84, 185] and/or gender [78, 82, 93, 107] on micronutrient status in people with DS, of which most were related to blood Zn measures. These studies showed that females and males with DS do not differ in Zn levels. However evidence was not conclusive with regards to the effect of age on Zn levels. One study showed that compared with healthy children without DS, children with DS had lower Zn levels, which were closely comparable to those observed in

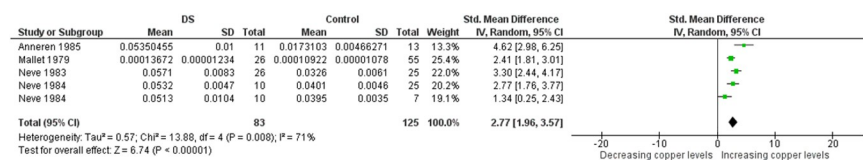


Fig 8. Meta-analysis of intra-erythrocyte levels of copper.

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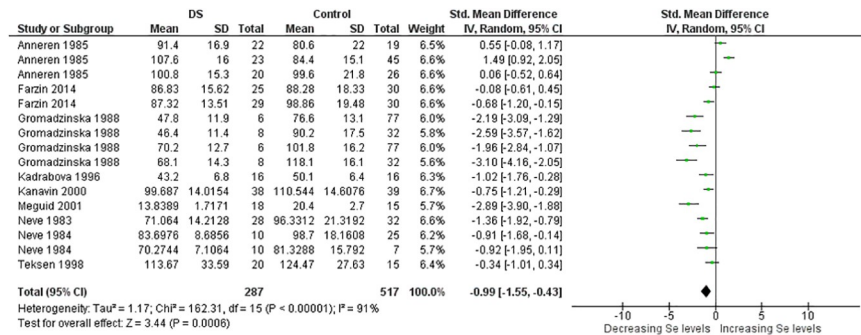


Fig 9. Meta-analysis of blood levels of selenium.

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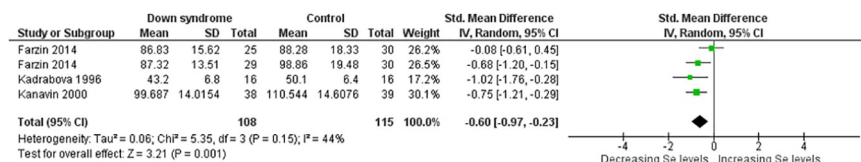


Fig 10. Meta-analysis of serum levels of selenium.

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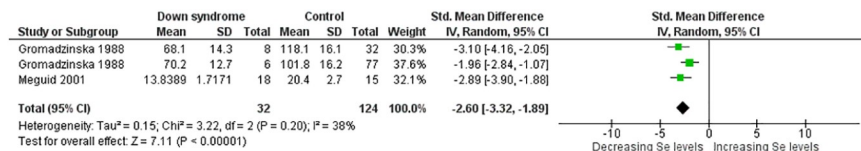


Fig 11. Meta-analysis of whole blood levels of selenium.

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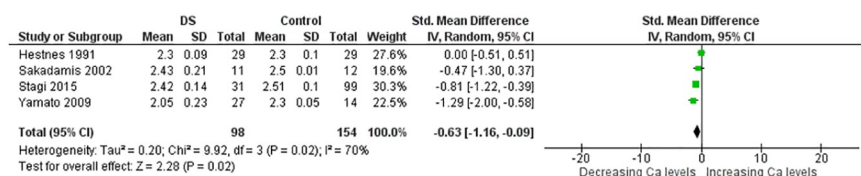


Fig 12. Meta-analysis of blood levels of calcium.

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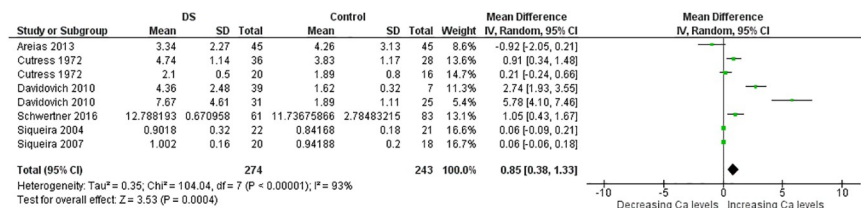


Fig 13. Meta-analysis of salivary levels of calcium.

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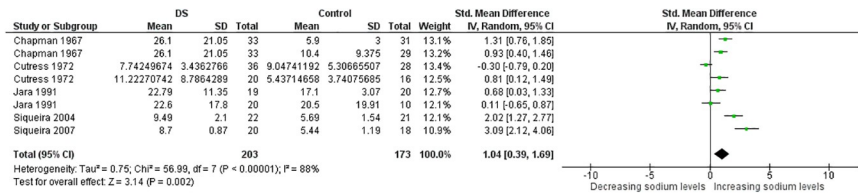


Fig 14. Meta-analysis of salivary levels of sodium.

<https://doi.org/10.1371/journal.pone.0175437.g014>

elderly healthy people without DS [84]. Additionally, one study demonstrated that Se concentrations in plasma and erythrocyte tend to increase with age in people with and without DS. They also tend to be higher in women than men [108]. Other studies indicated no effect of age or gender.

Future directions

A limitation of all such meta-analyses is that they cannot directly clarify the cause and effect. More clearly it has not been answered yet whether micronutrient differences in people with DS are a result of their sedentary behavior and nutritional intake, as DS is a condition associated with decreased nutrient needs and limited exercise capacity [186], or a characteristic of the Syndrome like their different growth pattern. In the former case, longitudinal studies monitoring micronutrient measures and their relationship with clinical status and intake in people with DS may address this issue. The latter case raises a series of fundamental questions based on previous experiences about amino acid abnormalities and thyroid dysfunction which, as mentioned above, are considered a characteristic of DS which normalization by treatment has been proven ineffective in improving their clinical status. Thus fundamental, observational or clinical studies may reveal a. whether the micronutrient profile in DS is correlated with clinical status or QoL, b. whether micronutrient supplements are able to improve these. As it remains a likely possibility that a specific different physiological pattern of amino acids, hormones and micronutrients does reflect DS.

Supporting information

S1 PRISMA Checklist. PRISMA checklist.

(DOC)

S1 Text. Search strategy.

(DOCX)

S1 Table. Trace elements and Down syndrome.

(DOCX)

S2 Table. Minerals and Down syndrome.

(DOCX)

S3 Table. Vitamins and Down syndrome.

(DOCX)

S4 Table. Summary of meta-analyses.

(DOCX)

S1 Fig. PRISMA flow diagram.

(DOC)

Author Contributions

Conceptualization: AS MM NR.

Data curation: AS.

Formal analysis: AS.

Investigation: AS NR.

Methodology: AS NR.

Project administration: NR AS.

Software: AS.

Supervision: NR.

Validation: AS.

Visualization: AS MM ADA NOR NR.

Writing – original draft: AS.

Writing – review & editing: AS MM ADA NOR NR.

References

1. Allen EG, Freeman SB, Druschel C, Hobbs CA, O'Leary LA, Romitti PA, et al. Maternal age and risk for trisomy 21 assessed by the origin of chromosome nondisjunction: a report from the Atlanta and National Down Syndrome Projects. *Human genetics*. 2009; 125(1):41–52. <https://doi.org/10.1007/s00439-008-0603-8> PMID: 19050929
2. James SJ, Pogribna M, Pogribny IP, Melnyk S, Hine RJ, Gibson JB, et al. Abnormal folate metabolism and mutation in the methylenetetrahydrofolate reductase gene may be maternal risk factors for Down syndrome. *The American journal of clinical nutrition*. 1999; 70(4):495–501. PMID: 10500018
3. Haddow JE, Palomaki GE, Knight GJ, Williams J, Pulkkinen A, Canick JA, et al. Prenatal screening for Down's syndrome with use of maternal serum markers. *New England journal of medicine*. 1992; 327(9):588–93. <https://doi.org/10.1056/NEJM199208273270902> PMID: 1379344
4. Roizen NJ, Patterson D. Down's syndrome. *The Lancet*. 2003; 361(9365):1281–9.
5. Palomaki GE, Kloza EM, Lambert-Messerlian GM, Haddow JE, Neveux LM, Ehrlich M, et al. DNA sequencing of maternal plasma to detect Down syndrome: an international clinical validation study. *Genetics in medicine*. 2011; 13(11):913–20. <https://doi.org/10.1097/GIM.0b013e3182368a0e> PMID: 22005709
6. Natoli JL, Ackerman DL, McDermott S, Edwards JG. Prenatal diagnosis of Down syndrome: a systematic review of termination rates (1995–2011). *Prenatal diagnosis*. 2012; 32(2):142–53. <https://doi.org/10.1002/pd.2910> PMID: 22418958
7. Sherman SL, Allen EG, Bean LH, Freeman SB. Epidemiology of Down syndrome. *Mental retardation and developmental disabilities research reviews*. 2007; 13(3):221–7. <https://doi.org/10.1002/mrdd.20157> PMID: 17910090
8. van Gameren-Oosterom H, Buitendijk SE, Bilardo CM, Pal-de Bruin KM, Van Wouwe JP, Mohangoo AD. Unchanged prevalence of Down syndrome in the Netherlands: results from an 11-year nationwide birth cohort. *Prenatal diagnosis*. 2012; 32(11):1035–40. <https://doi.org/10.1002/pd.3951> PMID: 22865545
9. Bittles AH, Bower C, Hussain R, Glasson EJ. The four ages of Down syndrome. *The European Journal of Public Health*. 2007; 17(2):221–5. <https://doi.org/10.1093/eurpub/ckl103> PMID: 16857692
10. Englund A, Jonsson B, Zander CS, Gustafsson J, Annerén G. Changes in mortality and causes of death in the Swedish Down syndrome population. *American Journal of Medical Genetics Part A*. 2013; 161(4):642–9.
11. Lott IT, Dierssen M. Cognitive deficits and associated neurological complications in individuals with Down's syndrome. *The Lancet Neurology*. 2010; 9(6):623–33. [https://doi.org/10.1016/S1474-4422\(10\)70112-5](https://doi.org/10.1016/S1474-4422(10)70112-5) PMID: 20494326

12. Kent L, Evans J, Paul M, Sharp M. Comorbidity of autistic spectrum disorders in children with Down syndrome. *Developmental Medicine & Child Neurology*. 1999; 41(3):153–8.
13. Lai F, Williams RS. A prospective study of Alzheimer disease in Down syndrome. *Archives of neurology*. 1989; 46(8):849–53. PMID: [2527024](#)
14. Rubin SS, Rimmer JH, Chicoine B, Braddock D, McGuire DE. Overweight prevalence in persons with Down syndrome. *Mental retardation*. 1998; 36(3):175–81. [https://doi.org/10.1352/0047-6765\(1998\)036<0175:OPIPWD>2.0.CO;2](https://doi.org/10.1352/0047-6765(1998)036<0175:OPIPWD>2.0.CO;2) PMID: [9638037](#)
15. Cronk C, Crocker AC, Pueschel SM, Shea AM, Zackai E, Pickens G, et al. Growth charts for children with Down syndrome: 1 month to 18 years of age. *Pediatrics*. 1988; 81(1):102–10. PMID: [2962062](#)
16. Milunsky A, Neurath PW. Diabetes mellitus in Down's syndrome. *Archives of Environmental Health: An International Journal*. 1968; 17(3):372–6.
17. Karlsson B, Gustafsson J, Hedov G, Ivarsson SA, Annerén G. Thyroid dysfunction in Down's syndrome: relation to age and thyroid autoimmunity. *Archives of disease in childhood*. 1998; 79(3):242–5. PMID: [9875020](#)
18. Tu J- B, Zellweger H. BLOOD-SEROTONIN DEFICIENCY IN DOWN'S SYNDROME. *The Lancet*. 286(7415):715–7.
19. Rosner F, Ong B, Paine R, Mahanand D. BLOOD-SEROTONIN ACTIVITY IN TRISOMIC AND TRANSLOCATION DOWN'S SYNDROME. *The Lancet*. 1965; 285(7397):1191–3.
20. Lejeune J, Rethore MO, de Blois MC, Peeters M, Naffah J, Megarbane A, et al. [Amino acids and trisomy 21]. *Annales de genetique*. 1992; 35(1):8–13. Epub 1992/01/01. PMID: [1535189](#)
21. Heggarty HJ, Ball R, Smith M, Henderson MJ. Amino acid profile in Down's syndrome. *Archives of disease in childhood*. 1996; 74(4):347–9. PMID: [8669939](#)
22. Reynolds GP, Warner CEJ. Amino acid neurotransmitter deficits in adult Down's syndrome brain tissue. *Neuroscience letters*. 1988; 94(1–2):224–7. PMID: [2907377](#)
23. Van Trotsenburg ASP, Vulmsa T, van Rozenburg-Marres SLR, van Baar AL, Ridder JCD, Heymans HSA, et al. The effect of thyroxine treatment started in the neonatal period on development and growth of two-year-old Down syndrome children: a randomized clinical trial. *The Journal of Clinical Endocrinology & Metabolism*. 2005; 90(6):3304–11.
24. Hsiang YHH, Berkovitz GD, Bland GL, Migeon CJ, Warren AC, Opitz JM, et al. Gonadal function in patients with Down syndrome. *American journal of medical genetics*. 1987; 27(2):449–58. <https://doi.org/10.1002/ajmg.1320270223> PMID: [2955699](#)
25. Partington MW, MacDonald MRA, Tu JB. 5-Hydroxytryptophan (5-HTP) in Down's Syndrome. *Developmental Medicine & Child Neurology*. 1971; 13(3):362–72.
26. Fang Y-Z, Yang S, Wu G. Free radicals, antioxidants, and nutrition. *Nutrition (Burbank, Los Angeles County, Calif)*. 2002; 18(10):872–9.
27. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Annals of internal medicine*. 2009; 151(4):264–9. PMID: [19622511](#)
28. Saghazadeh A, Rezaei N. Brain-Derived Neurotrophic Factor Levels in Autism: A Systematic Review and Meta-Analysis. *Journal of Autism and Developmental Disorders*. 2017; 47(4):1018–29. <https://doi.org/10.1007/s10803-016-3024-x> PMID: [28138831](#)
29. Garaiova I, Muchova J, Sustrova M, Blazicek P, Sivonova M, Kvasnicka P, et al. The relationship between antioxidant systems and some markers of oxidative stress in persons with Down syndrome. *Biologia*. 2004; 59(6):787–94.
30. Jovanovic SV, Clements D, MacLeod K. Biomarkers of oxidative stress are significantly elevated in Down syndrome. *Free radical biology & medicine*. 1998; 25(9):1044–8. Epub 1998/12/31.
31. Licastro F, Mariani RA, Faldella G, Carpenè E, Guidicini G, Rangoni A, et al. Immune-endocrine status and coeliac disease in children with Down's syndrome: Relationships with zinc and cognitive efficiency. *Brain research bulletin*. 2001; 55(2):313–7. PMID: [11470333](#)
32. Lima AS, Cardoso BR, Cozzolino SF. Nutritional status of zinc in children with Down syndrome. *Biological trace element research*. 2010; 133(1):20–8. Epub 2009/05/27. <https://doi.org/10.1007/s12011-009-8408-8> PMID: [19468695](#)
33. Lloret A, Calzone R, Dunster C, Manini P, d'Ischia M, Degan P, et al. Different patterns of in vivo pro-oxidant states in a set of cancer- or aging-related genetic diseases. *Free radical biology & medicine*. 2008; 44(4):495–503. Epub 2007/12/07.
34. Lockitch G, Singh VK, Puterman ML, Godolphin WJ, Sheps S, Tingle AJ, et al. Age-related changes in humoral and cell-mediated immunity in Down syndrome children living at home. *Pediatric research*. 1987; 22(5):536–40. Epub 1987/11/01. <https://doi.org/10.1203/00006450-198711000-00013> PMID: [2960948](#)

35. Roizen NJ, Amarose AP. Hematologic abnormalities in children with Down syndrome. *American journal of medical genetics*. 1993; 46(5):510–2. Epub 1993/06/15. <https://doi.org/10.1002/ajmg.1320460509> PMID: 8322810
36. Storm W. Hypercarotenemia in children with Down's syndrome. *Journal of mental deficiency research*. 1990; 34 (Pt 3):283–6. Epub 1990/06/01.
37. Biselli JM, Zampieri BL, Goloni-Bertollo EM, Haddad R, Fonseca MF, Eberlin MN, et al. Genetic polymorphisms modulate the folate metabolism of Brazilian individuals with Down syndrome. *Molecular biology reports*. 2012; 39(10):9277–84. Epub 2012/08/21. <https://doi.org/10.1007/s11033-012-1629-5> PMID: 22903356
38. El-Gendy H, Mokhtar HM. Homocysteine, an indicator of methylation pathway alternation in Down syndrome and its regulation by folic acid therapy. *Journal of Research in Medical Sciences*. 2007; 12 (2):86–9.
39. Jackson CV, Holland AJ, Williams CA, Dickerson JW. Vitamin E and Alzheimer's disease in subjects with Down's syndrome. *Journal of mental deficiency research*. 1988; 32 (Pt 6):479–84. Epub 1988/12/01.
40. Marreiro DdN, de Sousa AF, Nogueira NdN, Oliveira FE. Effect of Zinc Supplementation on Thyroid Hormone Metabolism of Adolescents with Down Syndrome. *Biological trace element research*. 2009; 129(1–3):20–7. <https://doi.org/10.1007/s12011-008-8280-y> PMID: 19050829
41. Mendes CC, Raimundo AM, Oliveira LD, Zampieri BL, Marucci GH, Biselli JM, et al. DHFR 19-bp deletion and SHMT C1420T polymorphisms and metabolite concentrations of the folate pathway in individuals with Down syndrome. *Genetic testing and molecular biomarkers*. 2013; 17(4):274–7. Epub 2013/02/21. PubMed Central PMCID: PMC3609604. <https://doi.org/10.1089/gtmb.2012.0293> PMID: 23421317
42. Nordstrom M, Paus B, Andersen LF, Kolset SO. Dietary aspects related to health and obesity in Williams syndrome, Down syndrome, and Prader-Willi syndrome. *Food & nutrition research*. 2015; 59:25487. Epub 2015/02/06. PubMed Central PMCID: PMC364317472.
43. Soler Marin A, Xandri Graupera JM. Nutritional status of intellectual disabled persons with Down syndrome. *Nutricion hospitalaria*. 2011; 26(5):1059–66. Epub 2011/11/11. <https://doi.org/10.1590/S0212-16112011000500021> PMID: 22072353
44. Tenenbaum A, Malkiel S, Wexler ID, Levy-Khademi F, Revel-Vilk S, Stepensky P. Anemia in children with down syndrome. *International journal of pediatrics*. 2011; 2011:813541. Epub 2011/09/24. PubMed Central PMCID: PMC3173951. <https://doi.org/10.1155/2011/813541> PMID: 21941570
45. Neve J, Molle L, Hanocq M, Sinet PM, Van Geffel R. Erythrocyte and plasma trace element levels in clinical assessments: Zinc, copper, and selenium in normals and patients with Down's syndrome and cystic fibrosis. *Biological trace element research*. 1983; 5(2):75–9. Epub 1983/04/01. <https://doi.org/10.1007/BF02916627> PMID: 24263449
46. Anneren G, Gebre-Medhin M. Trace elements and transport proteins in serum of children with Down syndrome and of healthy siblings living in the same environment. *Human nutrition Clinical nutrition*. 1987; 41(4):291–9. Epub 1987/07/01. PMID: 2442124
47. Anneren G, Gebre-Medhin M, Gustavson KH. Increased plasma and erythrocyte selenium concentrations but decreased erythrocyte glutathione peroxidase activity after selenium supplementation in children with Down syndrome. *Acta paediatrica Scandinavica*. 1989; 78(6):879–84. Epub 1989/11/01. PMID: 2532445
48. Baeteman MA, Mattei MG, Baret A, Mattei JF. Immunoreactive copper-zinc superoxide-dismutase (SOD-1) in mosaic trisomy 21 and normal subjects. *Acta paediatrica Scandinavica*. 1984; 73(3):341–4. Epub 1984/05/01. PMID: 6234750
49. Bjorksten B, Back O, Gustavson KH, Hallmans G, Hagglof B, Tarnvik A. Zinc and immune function in Down's syndrome. *Acta paediatrica Scandinavica*. 1980; 69(2):183–7. Epub 1980/03/01. PMID: 6445155
50. Bruhl HH, Foni J, Lee YH, Madow A. Plasma concentrations of magnesium, lead, lithium, copper, and zinc in mentally retarded persons. *American journal of mental deficiency*. 1987; 92(1):103–11. Epub 1987/07/01. PMID: 2956883
51. Carratelli M, Porcaro L, Ruscica M, De Simone E, Bertelli AA, Corsi MM. Reactive oxygen metabolites and prooxidant status in children with Down's syndrome. *International journal of clinical pharmacology research*. 2001; 21(2):79–84. Epub 2002/02/05. PMID: 11824651
52. Cengiz M, Seven M, Cengiz S, Yuksel A, Iscan MY. Vitamin and mineral status in Down syndrome. *Trace Elements and Electrocytes*. 2000; 17(3):156–60.
53. Center J, Beange H, McElduff A. People with mental retardation have an increased prevalence of osteoporosis: a population study. *American journal of mental retardation: AJMR*. 1998; 103(1):19–28.

- Epub 1998/07/25. [https://doi.org/10.1352/0895-8017\(1998\)103<0019:PWMRHA>2.0.CO;2](https://doi.org/10.1352/0895-8017(1998)103<0019:PWMRHA>2.0.CO;2) PMID: 9678227
54. Ciaccio M, Piccione M, Giuffre M, Macaione V, Vocca L, Bono A, et al. Aminoacid profile and oxidative status in children affected by Down syndrome before and after supplementary nutritional treatment. *The Italian journal of biochemistry*. 2003; 52(2):72–9. Epub 2003/12/18. PMID: 14677423
 55. Colombo ML, Girardo E, Incarbone E, Conti R, Ricci BM, Maina D. [Vitamin C in children with trisomy 21]. *Minerva pediatrica*. 1989; 41(4):189–92. Epub 1989/04/01. PMID: 2528054
 56. Colombo ML, Girardo E, Incarbone E, Conti R, Ricci BM, Maina D. Ascorbic acid in children with Down's syndrome. *Minerva pediatrica*. 1989; 41(4):189–92. PMID: 2528054
 57. Colombo ML, Givvardo E, Ricci BM, Maina D. [Blood zinc in patients with Down's syndrome and its relations with their immune status]. *Minerva pediatrica*. 1989; 41(2):71–5. Epub 1989/02/01. PMID: 2525662
 58. Concolino D, La Gamba G, Pelaggi P, Pascuzzi A, Pietragalla E, Bonapace G, et al. Macrocytosis despite low iron and ferritin concentrations in Down's Syndrome. *Italian journal of pediatrics*. 2001; 27(5):791–3.
 59. Frischer H, Chu LK, Ahmad T, Justice P, Smith GF. Superoxide dismutase and glutathione peroxidase abnormalities in erythrocytes and lymphoid cells in Down syndrome. *Progress in clinical and biological research*. 1981; 55:269–89. Epub 1981/01/01. PMID: 6457303
 60. Gericke GS, Hesseling PB, Brink S, Tiedt FC. Leucocyte ultrastructure and folate metabolism in Down's syndrome. *South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde*. 1977; 51(12):369–74. Epub 1977/03/19. PMID: 139696
 61. Ibarra B, Rivas F, Medina C, Franco Ma E, Romero-Garcia F, Enriquez C, et al. Hematological and biochemical studies in children with Down syndrome. *Annales de genetique*. 1990; 33(2):84–7. PMID: 1700661
 62. Kamiński K, Oyanagui Y, Królak B, Schuścik M. Superoxide dismutase activity in plasma and erythrocytes of children with trisomy 21 and their parents. *Pediatrics and Related Topics*. 1996; 35(1):49–53.
 63. Licastro F, Mocchegiani E, Masi M, Fabris N. Modulation of the neuroendocrine system and immune functions by zinc supplementation in children with Down's syndrome. *Journal of trace elements and electrolytes in health and disease*. 1993; 7(4):237–9. Epub 1993/12/01. PMID: 8019155
 64. Matin MA, Sylvester PE, Edwards D, Dickerson JWT. Vitamin and zinc status in Down syndrome. *Journal of mental deficiency research*. 1981; 25(2):121–6.
 65. Palmer S. Influence of vitamin A nutriture on the immune response: findings in children with Down's syndrome. *International journal for vitamin and nutrition research Internationale Zeitschrift fur Vitamin- und Ernährungsforschung Journal international de vitaminologie et de nutrition*. 1978; 48(2):188–216. Epub 1978/01/01. PMID: 151083
 66. Purice M, Maximilian C, Dumitriu I, Ioan D. Zinc and copper in plasma and erythrocytes of Down's syndrome children. *Endocrinologie*. 1988; 26(2):113–7. Epub 1988/04/01. PMID: 2970667
 67. Schmid F, Christeller S, Rehm W. [Studies on the state of vitamins B1, B2 and B6 in Down's syndrome]. *Fortschritte der Medizin*. 1975; 93(25):1170–2. Epub 1975/09/11. PMID: 129424
 68. Schmid F, Christeller S, Rehm W. Vitamin B1, B2 and B6 in Down syndrome. *Fortschritte der Medizin*. 1975; 93(25):1170–2. PMID: 129424
 69. Shah SN, Johnson RC, Singh VN. Antioxidant vitamin levels, lipid peroxidation, and immune status in Down's syndrome subjects. *Annals of the New York Academy of Sciences*. 1990; 587:313–5.
 70. Sinet PM, Neve J, Nicole A, Molle L. Low plasma selenium in Down's syndrome (trisomy 21). *Acta paediatrica Scandinavica*. 1984; 73(2):275–7. PMID: 6234748
 71. Solomon BD. Commentary on: Expression of cystathionine beta-synthase and histopathological observations in placentas of patients with Down syndrome. *Journal of Neonatal-Perinatal Medicine*. 2015; 8(2):73–5. <https://doi.org/10.3233/NPM-15915031> PMID: 26410428
 72. Song C, He J, Chen J, Liu Y, Xiong F, Wang Y, et al. Effect of the one-carbon unit cycle on overall DNA methylation in children with Down's syndrome. *Molecular medicine reports*. 2015; 12(6):8209–14. <https://doi.org/10.3892/mmr.2015.4439> PMID: 26497014
 73. Šustrová M, Krivošíková Z, Spustová V, Štefíková K. Vitamin D deficits in persons with down syndrome and early prevalence of osteoporosis. *Rheumatologia*. 2008; 22(3):87–94.
 74. Varga P, Oláh AV, Oláh É. Biochemical alterations in patients with Down syndrome. *Orvosi hetilap*. 2008; 149(26):1203–13. <https://doi.org/10.1556/OH.2008.28327> PMID: 18565815
 75. Wachowicz B, Kdziora J. [Low blood iron content in children with Down's syndrome]. *Endokrynologia Polska*. 1974; 25(1):9–13. Epub 1974/01/01. PMID: 4277223

76. Westermarck T, Antila E, Johansson E, Lindh U, Nordberg UR. Selenium supplementation and trace element alterations in Down's syndrome. *Journal of trace elements and electrolytes in health and disease*. 1993; 7(2):125–6.
77. Halsted J, Smith JC Jr. PLASMA-ZINC IN HEALTH AND DISEASE. *The Lancet*. 1970; 295(7642):322–4.
78. Milunsky A, Hackley BM, Halstead JA. Plasma, erythrocyte and leucocyte zinc levels in Down's syndrome. *Journal of mental deficiency research*. 1970; 14(2):99–105. PMID: [4254087](#)
79. Cutress TW. Composition, flow-rate and pH of mixed and parotid salivas from trisomic 21 and other mentally retarded subjects. *Archives of oral biology*. 1972; 17(7):1081–94. PMID: [4262797](#)
80. McBean LD, Smith JC Jr, Berne BH, Halsted JA. Serum zinc and alpha2-macroglobulin concentration in myocardial infarction, decubitus ulcer, multiple myeloma, prostatic carcinoma, down's syndrome and nephrotic syndrome. *Clinica Chimica Acta*. 1974; 50(1):43–51.
81. Tukiainen E, Tuomisto J, Westermarck T, Kupiainen H. Nature of lowered 5-hydroxytryptamine uptake by blood platelets of patients with Down's syndrome. *Acta pharmacologica et toxicologica*. 1980; 47(5):365–70. Epub 1980/11/01. PMID: [6457503](#)
82. Barlow PJ, Sylvester PE, Dickerson JW. Hair trace metal levels in Down syndrome patients. *Journal of mental deficiency research*. 1981; 25(Pt 3):161–8. Epub 1981/09/01. PMID: [6456356](#)
83. Neve J, Sinet PM, Molle L, Nicole A. Selenium, zinc and copper in Down's syndrome (trisomy 21): blood levels and relations with glutathione peroxidase and superoxide dismutase. *Clinica chimica acta; international journal of clinical chemistry*. 1983; 133(2):209–14. Epub 1983/09/30. PMID: [6226457](#)
84. Fabris N, Amadio L, Licastro F, Mocchegiani E, Zannotti M, Franceschi C. THYMIC HORMONE DEFICIENCY IN NORMAL AGEING AND DOWN'S SYNDROME: IS THERE A PRIMARY FAILURE OF THE THYMUS? *The Lancet*. 1984; 323(8384):983–6.
85. Neve J, Vertongen F, Cauchie P, Gnat D, Molle L. Selenium and glutathione peroxidase in plasma and erythrocytes of Down's syndrome (trisomy 21) patients. *Journal of mental deficiency research*. 1984; 28 (Pt 4):261–8. Epub 1984/12/01.
86. Anneren G, Johansson E, Lindh U. Trace element profiles in individual blood cells from patients with Down's syndrome. *Acta paediatrica Scandinavica*. 1985; 74(2):259–63. Epub 1985/03/01. PMID: [3158149](#)
87. Franceschi C, Chiricolo M, Licastro F, Zannotti M, Masi M, Mocchegiani E, et al. Oral zinc supplementation in Down's syndrome: restoration of thymic endocrine activity and of some immune defects. *Journal of mental deficiency research*. 1988; 32 (Pt 3):169–81. Epub 1988/06/01.
88. Kanavin O, Scott H, Fausa O, Ek J, Gaarder PI, Brandtzaeg P. Immunological studies of patients with Down's syndrome. Measurements of autoantibodies and serum antibodies to dietary antigens in relation to zinc levels. *Acta medica Scandinavica*. 1988; 224(5):473–7. Epub 1988/01/01. PMID: [2974234](#)
89. Noble RL, Warren RP. Analysis of blood cell populations, plasma zinc and natural killer cell activity in young children with Down's syndrome. *Journal of mental deficiency research*. 1988; 32 (Pt 3):193–201. Epub 1988/06/01.
90. Stabile A, Pesaresi MA, Stabile AM, Pastore M, Sopo SM, Ricci R, et al. Immunodeficiency and plasma zinc levels in children with Down's syndrome: a long-term follow-up of oral zinc supplementation. *Clinical immunology and immunopathology*. 1991; 58(2):207–16. Epub 1991/02/01. PMID: [1824686](#)
91. Licastro F, Mocchegiani E, Zannotti M, Arena G, Masi M, Fabris N. Zinc affects the metabolism of thyroid hormones in children with Down's syndrome: normalization of thyroid stimulating hormone and of reversal triiodothyronine plasmic levels by dietary zinc supplementation. *The International journal of neuroscience*. 1992; 65(1–4):259–68. Epub 1992/07/01. PMID: [1341688](#)
92. Rascon Trincado MV, Lorente Toledano F, Salazar -Villalobos AV. Evaluation of plasma zinc levels in patients with Down's syndrome. *Anales espanoles de pediatria*. 1992; 37(5):391–3. PMID: [1456622](#)
93. Licastro F, Chiricolo M, Mocchegiani E, Fabris N, Zannotti M, Beltrandi E, et al. Oral zinc supplementation in Down's syndrome subjects decreased infections and normalized some humoral and cellular immune parameters. *Journal of intellectual disability research: JIDR*. 1994; 38 (Pt 2):149–62. Epub 1994/04/01.
94. Sustrova M, Strbak V. Thyroid function and plasma immunoglobulins in subjects with Down's syndrome (DS) during ontogenesis and zinc therapy. *Journal of endocrinological investigation*. 1994; 17(6):385–90. Epub 1994/06/01. <https://doi.org/10.1007/BF03347724> PMID: [7930384](#)
95. Kadrabova J, Madaric A, Sustrova M, Ginter E. Changed serum trace element profile in Down's syndrome. *Biological trace element research*. 1996; 54(3):201–6. Epub 1996/09/01. <https://doi.org/10.1007/BF02784431> PMID: [8909693](#)

96. Toledo C, Alembik Y, Dott B, Finck S, Stoll C. [Anomalies of thyroid function in children with Down syndrome]. *Archives de pediatrie: organe officiel de la Societe francaise de pediatrie*. 1997; 4(2):116–20. Epub 1997/02/01.
97. Teksen F, Sayli BS, Aydin A, Sayal A, Isimer A. Antioxidative metabolism in Down syndrome. *Biological trace element research*. 1998; 63(2):123–7. Epub 1998/11/21. <https://doi.org/10.1007/BF02778871> PMID: 9823438
98. Kanavin OJ, Aaseth J, Birketvedt GS. Thyroid hypofunction in Down's syndrome: is it related to oxidative stress? *Biological trace element research*. 2000; 78(1–3):35–42. Epub 2001/04/21. <https://doi.org/10.1385/BTER:78:1-3:35> PMID: 11314986
99. Meguid NA, Kholoussi NM, Afifi HH. Evaluation of superoxide dismutase and glutathione peroxidase enzymes and their cofactors in Egyptian children with Down's syndrome. *Biological trace element research*. 2001; 81(1):21–8. Epub 2001/08/18. <https://doi.org/10.1385/BTER:81:1:21> PMID: 11508329
100. Soto-Quintana M, Alvarez-Nava F, Rojas-Atencio A, Granadillo V, Fernandez D, Ocando A, et al. [Diminished zinc plasma concentrations and alterations in the number of lymphocyte subpopulations in Down's syndrome patients]. *Investigacion clinica*. 2003; 44(1):51–60. Epub 2003/04/22. PMID: 12703183
101. Siqueira WL, de Oliveira E, Mustacchi Z, Nicolau J. Electrolyte concentrations in saliva of children aged 6–10 years with Down syndrome. *Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics*. 2004; 98(1):76–9. Epub 2004/07/10. <https://doi.org/10.1016/S107921040400277X> PMID: 15243474
102. Yenigun A, Ozkinay F, Cogulu O, Coker C, Cetiner N, Ozden G, et al. Hair zinc level in Down syndrome. *Down's syndrome, research and practice: the journal of the Sarah Duffen Centre / University of Portsmouth*. 2004; 9(2):53–7. Epub 2004/08/31.
103. Fernández DR, Vásquez ADC, Hernández M, Ocando AM, Manzanilla JG, Soto M, et al. Medical application of fast furnace program used in the ETA-AAS determination of Cu and Zn in blood plasma of children with down syndrome. *Atomic Spectroscopy*. 2005; 26(3):117–24.
104. Marques RC, de Sousa AF, do Monte SJ, Oliveira FE, do Nascimento Nogueira N, Marreiro DN. Zinc nutritional status in adolescents with Down syndrome. *Biological trace element research*. 2007; 120(1–3):11–8. Epub 2007/10/06. <https://doi.org/10.1007/s12011-007-0061-5> PMID: 17916950
105. Siqueira WL, Siqueira MF, Mustacchi Z, de Oliveira E, Nicolau J. Salivary parameters in infants aged 12 to 60 months with Down syndrome. *Special care in dentistry: official publication of the American Association of Hospital Dentists, the Academy of Dentistry for the Handicapped, and the American Society for Geriatric Dentistry*. 2007; 27(5):202–5. Epub 2007/11/10.
106. Meguid NA, Dardir AA, El-Sayed EM, Ahmed HH, Hashish AF, Ezzat A. Homocysteine and oxidative stress in Egyptian children with Down syndrome. *Clinical biochemistry*. 2010; 43(12):963–7. Epub 2010/05/11. <https://doi.org/10.1016/j.clinbiochem.2010.04.058> PMID: 20450901
107. Farzin L, Sajadi F, Kupai L. The Survey of Serum Trace Element Profiles in Down's Syndrome. *Zahedan Journal of Research in Medical Sciences*. 2014; 16(6):77–9.
108. Anneren G, Gebre-Medhin M, Gustavson KH, Plantin LO. Selenium in plasma and erythrocytes in patients with Down's syndrome and healthy controls. Variation in relation to age, sex and glutathione peroxidase activity in erythrocytes. *Acta paediatrica Scandinavica*. 1985; 74(4):508–14. Epub 1985/07/01. PMID: 3161267
109. Areias C, Sampaio-Maia B, Macho V, Leal I, Melo P, de Andrade C. Does the chemistry in the saliva of Down syndrome children explain their low caries prevalence? *European journal of paediatric dentistry: official journal of European Academy of Paediatric Dentistry*. 2013; 14(1):23–6. Epub 2013/04/20.
110. Barden HS. Vitamin A and carotene values of institutionalised mentally retarded subjects with and without Down's syndrome. *Journal of mental deficiency research*. 1977; 21(1):63–74. Epub 1977/03/01. PMID: 140939
111. Barden HS. Serum vitamin A and carotene levels in Down's syndrome and other retarded subjects showing enamel abnormalities of the permanent dentition. *Journal of mental deficiency research*. 1978; 22(3):213–21. Epub 1978/09/01. PMID: 151744
112. Bras A, Monteiro C, Rueff J. Oxidative stress in trisomy 21. A possible role in cataractogenesis. *Ophthalmic paediatrics and genetics*. 1989; 10(4):271–7. Epub 1989/12/01. PMID: 2534164
113. Chapman MJ, Donoghue EC, Saggars BA, Stern J. Parotid saliva sodium in Down's disease. *Journal of mental deficiency research*. 1967; 11(3):185–93. PMID: 4228461
114. Chávez CJ, Ortega P, Leal J, D'Escrivan A, González R, Miranda LE. Vitamin A deficiency and nutritional status in patients with Down's syndrome. *Anales de Pediatría*. 2010; 72(3):185–90. <https://doi.org/10.1016/j.anpedi.2009.10.024> PMID: 20153273

115. Coburn SP, Schaltenbrand WE, Mahuren JD, Clausman RJ, Townsend D. Effect of megavitamin treatment on mental performance and plasma vitamin B6 concentrations in mentally retarded young adults. *The American journal of clinical nutrition*. 1983; 38(3):352–5. Epub 1983/09/01. PMID: [6613909](#)
116. David O, Fiorucci GC, Tosi MT, Altare F, Valori A, Saracco P, et al. Hematological studies in children with Down syndrome. *Pediatric hematology and oncology*. 1996; 13(3):271–5. Epub 1996/05/01. PMID: [8735344](#)
117. Davidovich E, Aframian DJ, Shapira J, Peretz B. A comparison of the sialochemistry, oral pH, and oral health status of Down syndrome children to healthy children. *International journal of paediatric dentistry / the British Paedodontic Society [and] the International Association of Dentistry for Children*. 2010; 20(4):235–41. Epub 2010/06/12.
118. De Sousa MC, Vieira RB, Dos Santos DS, Carvalho CAT, Camargo SEA, Mancini MNG, et al. Antioxidants and biomarkers of oxidative damage in the saliva of patients with Down's syndrome. *Archives of oral biology*. 2015; 60(4):600–5. <https://doi.org/10.1016/j.archoralbio.2014.09.013> PMID: [25621938](#)
119. Del Arco C, Riancho JA, Luzuriaga C, Gonzalez-Macias J, Florez J. Vitamin D status in children with Down's syndrome. *Journal of intellectual disability research: JIDR*. 1992; 36 (Pt 3):251–7. Epub 1992/06/01.
120. Ercis M, Balci S, Atakan N. Dermatological manifestations of 71 Down syndrome children admitted to a clinical genetics unit. *Clinical genetics*. 1996; 50(5):317–20. Epub 1996/11/01. PMID: [9007317](#)
121. Fillon-Emery N, Chango A, Mircher C, Barbe F, Blehaut H, Herbeth B, et al. Homocysteine concentrations in adults with trisomy 21: effect of B vitamins and genetic polymorphisms. *The American journal of clinical nutrition*. 2004; 80(6):1551–7. Epub 2004/12/09. PMID: [15585767](#)
122. Garcez ME, Peres W, Salvador M. Oxidative stress and hematologic and biochemical parameters in individuals with Down syndrome. *Mayo Clinic proceedings*. 2005; 80(12):1607–11. Epub 2005/12/14. <https://doi.org/10.4065/80.12.1607> PMID: [16342654](#)
123. Garlet TR, Parisotto EB, de Medeiros GdS, Radin Pereira LC, Dison Machado Moreira EA, Dalmarco EM, et al. Systemic oxidative stress in children and teenagers with Down syndrome. *Life sciences*. 2013; 93(16):558–63. <https://doi.org/10.1016/j.lfs.2013.08.017> PMID: [24004546](#)
124. Gromadzińska J, Wasowicz W, Sklodowska M. Glutathione Peroxidase Activity, Lipid Peroxides and Selenium Status in Blood in Patients with Down's Syndrome. *Clinical chemistry and laboratory medicine*. 1988; 26(5):255–8.
125. Hestnes A, Stovner LJ, Husoy O, Folling I, Fougner KJ, Sjaastad O. Hormonal and biochemical disturbances in Down's syndrome. *Journal of mental deficiency research*. 1991; 35 (Pt 3):179–93. Epub 1991/06/01.
126. Howell A, Mason AS, Brown E, Watts RW, Chanarin I, McPherson K, et al. Red cell size and uric acid in Down's syndrome. *Scandinavian Journal of Haematology*. 1973; 11(2):140–7. PMID: [4272676](#)
127. Jara L, Ondarza A, Blanco R, Rivera L. Composition of the parotid saliva in Chilean children with Down's syndrome. *Archivos de biología y medicina experimentales*. 1991; 24(1):57–60. Epub 1991/01/01. PMID: [1845018](#)
128. Kedziora J, Bartosz G, Gromadzinska J, Sklodowska M, Wesowicz W, Scianowski J. Lipid peroxides in blood plasma and enzymatic antioxidative defence of erythrocytes in Down's syndrome. *Clinica chimica acta; international journal of clinical chemistry*. 1986; 154(3):191–4. Epub 1986/02/15. PMID: [2937579](#)
129. Licastro F, Marocchi A, Penco S, Porcellini E, Lio D, Dogliotti G, et al. Does Down's syndrome support the homocysteine theory of atherogenesis? Experience in elderly subjects with trisomy 21. *Archives of gerontology and geriatrics*. 2006; 43(3):381–7. Epub 2006/03/15. <https://doi.org/10.1016/j.archger.2006.01.003> PMID: [16533539](#)
130. Mallet B, Poulet P, Ayme S, Mattei MG, Mattei JF, Rebuffel P. Erythrocyte copper levels in children with trisomy 21. *Journal of mental deficiency research*. 1979; 23(3):219–25. Epub 1979/09/01. PMID: [159954](#)
131. Nandha Kumar S, Gane B, Ramachandra Rao K, Bhat VB. Folate and homocysteine metabolism in Indian children with Down syndrome. *Current Pediatric Research*. 2014; 18(1):11–4.
132. Obermann-Borst SA, van Driel LM, Helbing WA, de Jonge R, Wildhagen MF, Steegers EA, et al. Congenital heart defects and biomarkers of methylation in children: a case-control study. *European journal of clinical investigation*. 2011; 41(2):143–50. Epub 2010/09/28. <https://doi.org/10.1111/j.1365-2362.2010.02388.x> PMID: [20868449](#)
133. Pallardo FV, Degan P, d'Ischia M, Kelly FJ, Zatterale A, Calzone R, et al. Multiple evidence for an early age pro-oxidant state in Down Syndrome patients. *Biogerontology*. 2006; 7(4):211–20. Epub 2006/04/14. <https://doi.org/10.1007/s10522-006-9002-5> PMID: [16612664](#)

134. Parisotto EB, Garlet TR, de Liz Oliveira Cavalli VL, Zamoner A, da Rosa JS, Bastos J, et al. Antioxidant intervention attenuates oxidative stress in children and teenagers with Down syndrome. *Research in developmental disabilities*. 2014; 35(6):1228–36. <https://doi.org/10.1016/j.ridd.2014.03.013> PMID: 24685938
135. Parisotto EB, Giaretta AG, Zamoner A, Moreira EAM, Fröde TS, Pedrosa RC, et al. Persistence of the benefit of an antioxidant therapy in children and teenagers with Down syndrome. *Research in developmental disabilities*. 2015; 45–46:14–20. <https://doi.org/10.1016/j.ridd.2015.07.010> PMID: 26207872
136. Pastor MC, Sierra C, Dolade M, Navarro E, Brandi N, Cabre E, et al. Antioxidant enzymes and fatty acid status in erythrocytes of Down's syndrome patients. *Clinical chemistry*. 1998; 44(5):924–9. Epub 1998/05/20. PMID: 9590363
137. Pueschel SM, Hillemeier C, Caldwell M, Senft K, Mevs C, Pezzullo JC. Vitamin A gastrointestinal absorption in persons with Down's syndrome. *Journal of mental deficiency research*. 1990; 34 (Pt 3):269–75. Epub 1990/06/01.
138. Real de Asua D, Parra P, Costa R, Moldenhauer F, Suarez C. A cross-sectional study of the phenotypes of obesity and insulin resistance in adults with down syndrome. *Diabetes & metabolism journal*. 2014; 38(6):464–71. Epub 2014/12/30. PubMed Central PMCID: PMC4273033.
139. Sakadamis A, Angelopoulou N, Matziari C, Papameletiou V, Souftas V. Bone mass, gonadal function and biochemical assessment in young men with trisomy 21. *European journal of obstetrics, gynecology, and reproductive biology*. 2002; 100(2):208–12. Epub 2001/12/26. PMID: 11750967
140. Schwertner C, Santos Moreira MJ, Faccini LS, Hashizume LN. Biochemical composition of the saliva and dental biofilm of children with Down syndrome. *International Journal of Paediatric Dentistry*. 2016; 26(2):134–40. <https://doi.org/10.1111/ipd.12168> PMID: 25943195
141. Shah SN, Johnson RC. Antioxidant vitamin (A and E) status of Down's syndrome subjects. *Nutrition Research*. 1989; 9(7):709–15.
142. Stagi S, Lapi E, Romano S, Bargiacchi S, Brambilla A, Giglio S, et al. Determinants of vitamin d levels in children and adolescents with down syndrome. *International journal of endocrinology*. 2015; 2015:896758. Epub 2015/02/17. PubMed Central PMCID: PMC4320854. <https://doi.org/10.1155/2015/896758> PMID: 25685147
143. Sukla KK, Jaiswal SK, Rai AK, Mishra OP, Gupta V, Kumar A, et al. Role of folate-homocysteine pathway gene polymorphisms and nutritional cofactors in Down syndrome: A triad study. *Human reproduction (Oxford, England)*. 2015; 30(8):1982–93. Epub 2015/06/05.
144. Torsdottir G, Kristinsson J, Hreidarsson S, Snaedal J, Johannesson T. Copper, ceruloplasmin and superoxide dismutase (SOD1) in patients with Down's syndrome. *Pharmacology & toxicology*. 2001; 89(6):320–5. Epub 2002/03/21.
145. Yamato F, Takaya J, Yasuhara A, Teraguchi M, Ikemoto Y, Kaneko K. Elevated intracellular calcium in neutrophils in patients with Down syndrome. *Pediatrics international: official journal of the Japan Pediatric Society*. 2009; 51(4):474–7. Epub 2009/04/30.
146. Wells GA, Shea B, O'connell D, Peterson JEA, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2000.
147. Whittle N, Sartori SB, Dierssen M, Lubec G, Singewald N. Fetal Down syndrome brains exhibit aberrant levels of neurotransmitters critical for normal brain development. *Pediatrics*. 2007; 120(6):e1465–71. Epub 2007/11/14. <https://doi.org/10.1542/peds.2006-3448> PMID: 17998315
148. Coppus AW, Fekkes D, Verhoeven WM, Tuinier S, Egger JI, van Duijn CM. Plasma amino acids and neopterin in healthy persons with Down's syndrome. *Journal of neural transmission (Vienna, Austria: 1996)*. 2007; 114(8):1041–5. Epub 2007/04/03. PubMed Central PMCID: PMC42794348.
149. Wisniewski KE, Wisniewski HM, Wen GY. Occurrence of neuropathological changes and dementia of Alzheimer's disease in Down's syndrome. *Annals of neurology*. 1985; 17(3):278–82. <https://doi.org/10.1002/ana.410170310> PMID: 3158266
150. Giroux EL, Henkin RI. Competition for zinc among serum albumin and amino acids. *Biochimica et Biophysica Acta (BBA)—General Subjects*. 1972; 273(1):64–72.
151. Sharma SS, Dietz K-J. The significance of amino acids and amino acid-derived molecules in plant responses and adaptation to heavy metal stress. *Journal of Experimental Botany*. 2006; 57(4):711–26. <https://doi.org/10.1093/jxb/erj073> PMID: 16473893
152. Weitzdoerfer R, Stolzechner D, Dierssen M, Ferreres J, Fountoulakis M, Lubec G. Reduction of nucleoside diphosphate kinase B, Rab GDP-dissociation inhibitor beta and histidine triad nucleotide-binding protein in fetal Down syndrome brain. *Protein expression in Down Syndrome brain*. 2001; 61:347–59.
153. Bottino NR, Banks CH, Irgolic KJ, Micks P, Wheeler AE, Zingaro RA. Selenium containing amino acids and proteins in marine algae. *Phytochemistry*. 1984; 23(11):2445–52.

154. Sinet PM. Metabolism of oxygen derivatives in Down's syndrome. *Annals of the New York Academy of Sciences*. 1982; 396(1):83–94.
155. Agus ZS, Gardner LB, Beck LH, Goldberg M. Effects of parathyroid hormone on renal tubular reabsorption of calcium, sodium, and phosphate. *American Journal of Physiology—Legacy Content*. 1973; 224(5):1143.
156. Schneider P, Paunier L, Sizonenko PC, Wyss M. Effects of parathyroid hormone on total protein, calcium, magnesium, phosphorus, sodium and potassium concentrations of normal human parotid saliva. *European journal of clinical investigation*. 1977; 7(2):121–6. PMID: [404157](#)
157. Rabiei M, Masooleh IS, Leyli EK, Nikoukar LR. Salivary calcium concentration as a screening tool for postmenopausal osteoporosis. *International journal of rheumatic diseases*. 2013; 16(2):198–202. <https://doi.org/10.1111/1756-185X.12003> PMID: [23773645](#)
158. Angelopoulou N, Matziari C, Tsimaras V, Sakadamis A, Souftas V, Mandroukas K. Bone Mineral Density and Muscle Strength in Young Men with Mental Retardation (With and Without Down Syndrome). *Calcified Tissue International*. 2000; 66(3):176–80. PMID: [10666490](#)
159. Zubillaga P, Garrido A, Mugica I, Ansa J, Zabalza R, Emparanza JI. Effect of vitamin D and calcium supplementation on bone turnover in institutionalized adults with Down's Syndrome. *European journal of clinical nutrition*. 2006; 60(5):605–9. Epub 2006/01/05. <https://doi.org/10.1038/sj.ejcn.1602357> PMID: [16391575](#)
160. Coleman JE. Zinc proteins: enzymes, storage proteins, transcription factors, and replication proteins. *Annual review of biochemistry*. 1992; 61(1):897–946.
161. Tapiero H, Tew KD. Trace elements in human physiology and pathology: zinc and metallothioneins. *Biomedicine & Pharmacotherapy*. 2003; 57(9):399–411.
162. Stefanidou M, Maravelias C, Dona A, Spiliopoulou C. Zinc: a multipurpose trace element. *Archives of toxicology*. 2006; 80(1):1–9. Epub 2005/09/28. <https://doi.org/10.1007/s00204-005-0009-5> PMID: [16187101](#)
163. Ballestin R, Blasco-Ibanez JM, Crespo C, Nacher J, Lopez-Hidalgo R, Gilabert-Juan J, et al. Astrocytes of the murine model for Down Syndrome Ts65Dn display reduced intracellular ionic zinc. *Neurochemistry international*. 2014; 75:48–53. Epub 2014/06/10. <https://doi.org/10.1016/j.neuint.2014.05.013> PMID: [24911951](#)
164. Nose Y, Kim B- E, Thiele DJ. Ctr1 drives intestinal copper absorption and is essential for growth, iron metabolism, and neonatal cardiac function. *Cell Metabolism*. 2006; 4(3):235–44. <https://doi.org/10.1016/j.cmet.2006.08.009> PMID: [16950140](#)
165. Lott IT, Head E, Doran E, Busciglio J. Beta-amyloid, oxidative stress and down syndrome. *Current Alzheimer research*. 2006; 3(5):521–8. Epub 2006/12/16. PMID: [17168651](#)
166. Ordóñez FJ, Rosety M, Rosety-Rodríguez M. Regular exercise did not modify significantly superoxide dismutase activity in adolescents with Down's syndrome. *British journal of sports medicine*. 2006; 40(8):717–8. Epub 2006/07/26. PubMed Central PMCID: PMCPMC2579468. <https://doi.org/10.1136/bjism.2005.024315> PMID: [16864566](#)
167. Daniels LA. Selenium metabolism and bioavailability. *Biological Trace Element Research*. 1996; 54(3):185–99. <https://doi.org/10.1007/BF02784430> PMID: [8909692](#)
168. Schrauzer GN. Selenomethionine: A Review of Its Nutritional Significance, Metabolism and Toxicity. *The Journal of Nutrition*. 2000; 130(7):1653–6. PMID: [10867031](#)
169. Plum LM, Rink L, Haase H. The Essential Toxin: Impact of Zinc on Human Health. *International Journal of Environmental Research and Public Health*. 2010; 7(4):1342. <https://doi.org/10.3390/ijerph7041342> PMID: [20617034](#)
170. Fort P, Lifshitz F, Bellisario R, Davis J, Lanes R, Pugliese M, et al. Abnormalities of thyroid function in infants with Down syndrome. *The Journal of Pediatrics*. 1984; 104(4):545–9. PMID: [6231357](#)
171. Pueschel SM, Pezzullo JC. Thyroid dysfunction in down syndrome. *American Journal of Diseases of Children*. 1985; 139(6):636–9. PMID: [3159255](#)
172. King JC. Effect of low zinc intakes on basal metabolic rate, thyroid hormones and protein utilization in adult men. *J Nutr*. 1986; 116:1045–53. PMID: [3723200](#)
173. Kralik A, Eder K, Kirchgessner M. Influence of zinc and selenium deficiency on parameters relating to thyroid hormone metabolism. *Hormone and metabolic research*. 1996; 28(05):223–6.
174. Arthur JR, Nicol F, Beckett GJ. Selenium deficiency, thyroid hormone metabolism, and thyroid hormone deiodinases. *The American Journal of Clinical Nutrition*. 1993; 57(2):236S–9S.
175. Bucci I, Napolitano G, Giuliani C, Lio S, Minnucci A, Giacomo FD, et al. Zinc sulfate supplementation improves thyroid function in hypozincemic down children. *Biological Trace Element Research*. 1999; 67(3):257–68. PMID: [10201332](#)

176. Napolitano G, Palka G, Lio S, Bucci I, De Remigis P, Stuppia L, et al., editors. Is zinc deficiency a cause of subclinical hypothyroidism in Down syndrome? 1989.
177. Berger M, Reymond M, Shenkin A, Rey F, Wardle C, Cayeux C, et al. Influence of selenium supplements on the post-traumatic alterations of the thyroid axis: a placebo-controlled trial. *Intensive Care Medicine*. 2001; 27(1):91–100. PMID: [11280679](#)
178. Ram G, Chinen J. Infections and immunodeficiency in Down syndrome. *Clinical & Experimental Immunology*. 2011; 164(1):9–16.
179. Burgio GR, Ugazio A, Nespoli L, Maccario R. Down syndrome: a model of immunodeficiency. *Birth defects original article series*. 1983; 19(3):325. PMID: [6228272](#)
180. Bonaventura P, Benedetti G, Albarède F, Miossec P. Zinc and its role in immunity and inflammation. *Autoimmunity Reviews*. 2015; 14(4):277–85. <https://doi.org/10.1016/j.autrev.2014.11.008> PMID: [25462582](#)
181. Beck MA, Levander OA, Handy J. Selenium deficiency and viral infection. *The Journal of nutrition*. 2003; 133(5):1463S–7S.
182. Dworkin BM. Selenium deficiency in HIV infection and the acquired immunodeficiency syndrome (AIDS). *Chemico-biological interactions*. 1994; 91(2):181–6.
183. Harrison M, Fraser R. BONE STRUCTURE AND METABOLISM IN CALCIUM-DEFICIENT RATS. *Journal of Endocrinology*. 1960; 21(2):197–205.
184. Vogt K, Mellor J, Tong G, Nicoll R. The actions of synaptically released zinc at hippocampal mossy fiber synapses. *Neuron*. 2000; 26(1):187–96. PMID: [10798403](#)
185. Šustrová M, Štrbák V. Thyroid function and plasma immunoglobulins in subjects with Down's syndrome (DS) during ontogenesis and zinc therapy. *Journal of endocrinological investigation*. 1994; 17(6):385–90. <https://doi.org/10.1007/BF03347724> PMID: [7930384](#)
186. Millar AL, Fernhall B, Burkett LN. Effects of aerobic training in adolescents with Down syndrome. *Medicine & Science in Sports & Exercise*. 1993; 25(2):270–4.