Supplementary Material-A

In order to gather the relevant scientific literature, a search was conducted in Cochrane Central Register of Controlled Trials, MEDLINE, PubMed, Web of Science (WoS), Scopus, ScienceDirect (SD), and Embase database, without language restriction. The keyword search was performed using Boolean operators and wildcards. This involved the following steps:

- Search using the keywords “Down's syndrome”, “nutrition”, “toxicity”, and “heavy metals”;

- Examination limited to 50 recovered articles. Those potentially useful for this manuscript were selected while others which could not be used were discarded;

- Identification of 33 useful articles for this manuscript (covering the period from 1960 to 2020);

- Follow-up of some of the references cited in each article to complete the topic, leading to a total of 31 articles;

- Identification of 15 other articles not directly related to Down's syndrome but useful for documenting some concepts have been discussed in the main text and the Supplementary Information (SI); total of 79 articles.

First author **Year**	**Element** **Specimen**	**Study population (*N*)** **Male %** **Age**	**Study** **levels** **Mean (σ)**	**Control population (*N*)** **Male %** **Age**	**Control levels** **Mean (σ)**
Meguid 2001 Egypt		Down's Syndrome (DS) with trisomy 21 (*N* = 8)	14.2 (2.2)	Controls (*N* = 15) Range: 9-36 months	20.4 (2.7)

	Selenium Whole blood	Range: 9-36 months			
		DS (de novo translocations 21/22 (*N* = 3) and 21/21 (*N* = 2)) (*N* = 5) Range: 11-33 months	13.9 (0.9)		
		DS (mosaicism) (*N* = 5) Range: 12-22 months	13.2 (1.2)		
		DS (*N* = 18) Range: 9-36 months	13.84 (1.72)		
	Copper Plasma	DS with trisomy 21 (*N* = 8) Range: 9-36 months	2.1 (0.8)	Controls (*N* = 15) Range: 9-36 months	1.2 (0.2)
		DS (de novo translocations 21/22 (*N* = 3) and 21/21 (*N* = 2)) (*N* = 5) Range: 11-33 months	2.8 (0.8)		
		DS (mosaicism) (*N* = 5) Range: 12-22 months	2.3 (0.3)		
		DS (*N* = 18)	2.35 (0.76)		

		Range: 9-36 months			
	Zinc Plasma	DS with trisomy 21 (*N* = 8) Range: 9-36 months	1.3 (0.6)	Controls (*N* = 15) Range: 9-36 months	1.2 (0.2)
		DS (de novo translocations 21/22 (*N* = 3) and 21/21 (*N* = 2)) (*N* = 5) Range: 11-33 months	1.2 (0.5)		
		DS (mosaicism) (*N* = 5) Range: 12-22 months	2.5 (1)		
		DS (*N* = 18) Range: 9-36 months	1.61 (0.9)		
Kanavin 2000 Norway	Selenium Serum	DS (*N* = 38) mean age (μ_{age}) ± standard deviation (σ): 33±11.1 years	1.2625 (0.1775)	Controls (*N* = 39)	1.4 (0.185)
	Zinc Serum		14.4 (2.8)		15.91 (2)
	Copper Serum		18.5 (3.2)		18.8 (3.2)

Teksen 1998 Turkey	Selenium Plasma	DS (*N* = 20) Range: 3-16 years	113.67 (33.59)	Controls (*N* = 15)	124.47 (27.63)
	Copper Plasma		0.94 (0.17)		1.08 (0.17)
	Zinc Plasma		1.44 (0.25)		1.46 (0.3)
Halsted 1970 USA	Zinc Plasma	DS (*N* = 10) Range: 6-13 years	64 (8)	Healthy (*N* = 26) Range: 3-13 years	89 (13)
Fabris 1984 Italy	Zinc Plasma	DS (*N* = 21) Range: 3-16 years	86.3 (18.33)	Normal controls (*N* = 11) Range: 3-25 years	105 (7.9599)
				Normal controls (*N* = 11) Range: 65-80 years	81.9 (11.28)
Milunsky 1970 US state	Zinc Plasma	DS (*N* = 10) Male %: 60 μ_{age} ± σ: 7.591 ± 2.209557 years	64 (7.5)	Healthy (*N* = 16) Male %: 43.75 μ_{age} ± σ: 8.7575 ± 2.103925 years	90 (12.4)

	Zinc Red cell	DS (*N* = 6) Male %: 33.33 μ_{age} ± σ: 7.168333 ± 2.640912 years	13.5 (2.4)	Healthy (*N* = 15) Male %: 46.67 μ_{age} ± σ: 8.8 ± 2.177154 years	9.5 (1.4)
	Zinc Leukocyte	DS (*N* = 4)	0.01437 (0.0014)	Healthy (*N* = 5)	0.00948 (0.00447)
Gromadzinska 1988 Poland	Selenium Whole blood Erythrocyte Plasma	DS (*N* = 6) Range: 6-16 years	70.2 (12.7)	Controls (*N* = 77) Range: 6-16 years	101.8 (16.2)
			116.5 (23.8)	Controls (*N* = 74) Range: 6-16 years	142.2 (31.5)
			47.8 (11.9)	Controls (*N* = 77) Range: 6-16 years	76.6 (13.1)
	Selenium Whole blood Erythrocyte	DS (*N* = 8) Range: 17-30 years	68.1 (14.3)	Controls (*N* = 32) Range: 17-30 years	118.1 (16.1)
			110.3 (37.5)	Controls (*N* = 32) Range: 17-30 years	167.3 (33.3)

	Plasma		46.4 (11.4)	Controls (*N* = 32) Range: 17-30 years	90.2 (17.5)
Kedziora 1986 Poland	Selenium Erythrocytes	DS (*N* = 14)	1.6 (0.28)	Healthy (*N* = 81)	2.15 (0.46)
L. Farzin 2014	Iron	DS (*N* = 54) Range: 6-38 years	87.1 (14.31)	Healthy (*N* = 60) Range: 6-40 years	94.1 (19.47)
Neve 1983 France	Selenium Plasma Erythrocyte	DS (*N* = 28) DS (*N* = 28)	0.9 (0.18) 4.67 (1.12)	Healthy (*N* = 32) Healthy (*N* = 32)	1.22 (0.27) 4.34 (0.82)
	Zinc Plasma Erythrocyte	DS (*N* = 29) DS (*N* = 28)	13.5 (3.5) 679 (73)	Healthy (*N* = 32) Healthy (*N* = 31)	13 (2) 382 (84)
	Copper Plasma Erythrocyte	DS (*N* = 26) DS (*N* = 26)	23.5 (6.5) 57.1 (8.3)	Healthy (*N* = 25) Healthy (*N* = 25)	20.8 (5.5) 32.6 (6.1)
Meguid 2010	Zinc	DS (*N* = 42)	72.3 (9.6)	Healthy (*N* = 48)	98.5 (3.08)

Egypt	Serum	μ_{age} ± σ: 5 ± 1.1 years		μ_{age} ± σ: 5.6 ± 2 years	
	Copper Serum	DS (*N* = 42) μ_{age} ± σ: 5 ± 1.1 years	120 (7.5)	Healthy (*N* = 48) μ_{age} ± σ: 5.6 ± 2 years	129 (10.6)
Siqueira 2007 US	Zinc Saliva	DS (*N* = 20) Range: 12-60 months	0.003 (0.0009)	Healthy (*N* = 18) Range: 12-60 months	0.003 (0.001)
Marques 2007 Brazil	Zinc Plasma Erythrocyte Urine	DS (*N* = 30) Male %: 53.33% Range: 10-19 years	67.6 (25.6) 49.2 (8.5) 244.3 (194.9)	Healthy (*N* = 32) Male %: 40.63% Mean: 13.47 years	68.9 (22.3) 35.9 (6.1) 200.3 (236.4)
Garcez 2005 Brazil	Iron Serum	DS (*N* = 50) Male %: 50% μ_{age} ± σ: 14.2 ± 6.62 (3-24) years	63.64 (27.27)	Control (*N* = 50) Male %: 50% μ_{age} ± σ: 14.2 ± 6.62 years	59.1 (18.2)
Yenigun 2004 Turkey	Zinc Hair	DS (*N* = 19) Range: 2-6 years	95.18 (56.1)	Typically developing control (*N* = 11) Range: 2-6 years	208.88 (152.37)

Siqueira 2004 Brazil	Zinc Saliva	DS (*N* = 22) Male %: 54.54 Range: 6-10 years	0.002 (0.0009)	Healthy (*N* = 21) Male %: 52.38 Range: 6-10 years	0.002 (0.0012)
Torsdottir 2001 Iceland	Copper Plasma	DS (*N* = 35) Male %: 77.143% Mean (range): 37 (18-53) years	16.1 (12.28)	Healthy (*N* = 35)	16.2 (11.6)
Kanavin 1988 Norway	Zinc Serum	DS (*N* = 38) Male %: 60.5% Median (range): 32 (16-62) years	13.725 (3.025)	Mentally retarded patients without DS (*N* = 39)	16.25 (1.9)
Kadrabova 1995 Slovak Republic	Selenium Serum	DS (trisomy 21) (*N* = 16) Range: 4-23 years	43.2 (1.7)	Controls (*N* = 16)	50.1 (1.6)
	Copper Serum		1.34 (0.2)		1.1 (0.2)
	Zinc Serum		0.83 (0.08)		0.96 (0.12)
	Magnesium		21.7 (1.6)		21 (1.6)

	Serum				
Stabile 1991 Italy	Zinc Serum	DS (N = 38) Male %: 57.9% μ_{age} ± σ: 7 ± 4.1 years	0.67 (0.15)	Healthy (N = 20) Male %: 55 % μ_{age} ± σ: 6.9 ± 4.4 years	1.02 (0.24)
Sustrova 1994 Slovakia	Zinc Serum	DS (N = 20) Range: 1-6 years	0.75 (0.13416)	Controls (N = 19) Range: 1-6 years	1.01 (0.1308)
		DS (N = 45) Range: 6-15 years	0.81 (0.13416)	Controls (N = 20) Range: 6-15 years	1.04 (0.18)
		DS (N = 40) Range: 15-35 years	0.92 (0.1265)	Controls (N = 20) Range: 15-35 years	1.04 (0.18)
David 1996 Italy	Iron Serum	DS (N = 17) Range: 2-5 years	72 (32.1)	Healthy (N = 23) Range: 2-5 years	71.5 (26.5)
		DS (N = 23) Range: 5-10 years	74 (25.1)	Healthy (N = 25) Range: 5-10 years	69.2 (20.2)
		DS (N = 10) Range: 10-15 years	84.2 (29.4)	Healthy (N = 20) Range: 10-15 years	89 (23.8)

Franceschi 1988 Italy	Zinc Plasma	DS (*N* = 18) Male %: 61.1% μ_{age} ± σ: 7 ± 0.83 years	85.8 (4.5) 71.3 (3.4)	Healthy (*N* = 15) Male %: 60%	105.2 (2.4)
	Copper Plasma		74.8 (3.8) 67.9 (2.3)		71.4 (3.4)
Noble 1988 USA	Zinc Plasma	DS (*N* = 11)	1.5 (0.1)	Healthy (*N* = 11)	1.27 (0.05)
Toledo 1997 France	Zinc Serum	DS (*N* = 105) Male %: 47.6% Range: 3months-20 years	14.89 (1.65)	Control (*N* = 105)	19.04 (1.74)
Anneren 1985 Sweden	Selenium Plasma	DS (*N* = 65) Male %: 50.8% Range: 1 months-56 years	100 (17.3)	Healthy (*N* = 90) Male %: 58.9% Range: 2 months-54 years	87.9 (20.2)
	Selenium Erythrocyte		100 (17.3)		87.9 (20.2)
Anneren 1985 Sweden	Copper Erythrocyte	DS (*N* = 11) Male %: 72.73% Range: 4-10 years	3.4 (.06)	Healthy (*N* = 13) Male %: 46.2% Range: 5-14 years	1.1 (0.3)
	Zinc		8.5 (7.4)		17 (4.4)

	Erythrocyte				
	Fe Erythrocyte		320 (125.9)		560 (.2963)
	Manganese Erythrocyte		1 (0.15)		1.4 (0.4)
Neve 1984 Belgium	Zinc Plasma	DS (*N* = 10) Range: 21-51 years	11.9 (2) 691 (72)	Healthy (*N* = 25) Range: 23-57 years	15 (3.3)
	RBC	DS (*N* = 10) Range: 23-52 years	12.7 (1.5) 687 (73)	Healthy (*N* = 7) Range: 24-49 years	12.7 (1.8) 549 (70)
	Copper Plasma	DS (*N* = 10) Range: 21-51 years	17 (4.4) 53.2 (4.7)	Healthy (*N* = 25) Range: 23-57 years	19.7 (3.6) 40.1 (4.6)
	RBC	DS (*N* = 10) Range: 23-52 years	17.1 (4.2) 51.3 (10.4)	Healthy (*N* = 7) Range: 24-49 years	18.2 (5) 39.5 (3.5)
	Selenium Plasma	DS (*N* = 10) Range: 21-51 years	1.06 (0.11) 5.76 (0.82)	Healthy (*N* = 25) Range: 23-57 years	1.25 (0.23) 6.28 (0.89)
	RBC	DS (*N* = 10)	0.89 (0.09)	Healthy (*N* = 7)	1.03 (0.2)

		Range: 23-52 years	4.48 (0.94)	Range: 24-49 years	5.53 (0.66)
McBean 1974 USA	Zinc Serum	DS (*N* = 9) Male %: 44.44 μ_{age} ± σ: 34 ± 8 years	98 (16)	Controls (*N* = 20) Male %: 50 μ_{age} ± σ: 32 ± 10.198 years	101 (15)
Cutress 1972 New Zealand	Zinc Manganese Copper Fe Whole saliva	DS (*N* = 31) Range: 6-22 years	0.8 (0.4) 0.02 (0.02) 0.36 (0.18) 0.61 (0.81)	Non-trisomy mentally retarded (*N* = 28) Male %: 57.14 Range: 6-22 years	0.6 (0.6) 0.02 (0.01) 0.18 (0.11) 0.6 (1.06)
	Zinc Manganese Copper Fe Parotid saliva	DS (*N* = 16) Range: 7-22 years	0.2 (0.3) 0.01 (0.01) 0.31 (0.17) 0.07 (0.03)	Non-trisomy mentally retarded (*N* = 16) Male %: 50 Range: 8-23 years	0.6 (0.6) 0.02 (0.01) 0.48 (0.17) 0.15 (0.03)

Fernández 2005 Venezuela	Zinc Plasma	DS (*N* = 35) Range: 6 months-6 years	1839 (361)	Healthy (*N* = 35) Range: 6 mon-6 years	1374 (867)
	Copper Plasma		805 (261)		767 (288)
Soto-Quintana 2003 Venezuela	Zinc Plasma	DS (*N* = 43) Male %: 51.16% μ_{age} ± σ: 2.3 ± 2 years	809 (228.9)	Healthy (*N* = 40) Male %: 50% μ_{age} ± σ: 2.3 ± 2 years	1034.6 (166.9)
Licastro 1992 Italy	Zinc Plasma	DS (*N* = 25) Male %: 76 Range: 6-15 years	76 (3)	Normal controls (*N* = 14) Male %: 64.3% Range: 9-13 years	97 (4)
Barlow 1981 England	Zinc Copper Iron Manganese Hair	DS (*N* = 69) Male %: 100 μ_{age} ± σ: 39.4 ± 9.3 years	114.4 (30.8) 8.5 (3.1) 11.9 (8.3) 0.42 (0.35)	Normal controls (*N* = 35) Male %: 100 μ_{age} ± σ: 32.7 ± 20.1 years	120.3 (27.2) 24.2 (12.3) 24.4 (12.8) 2.67 (1.76)
				Patients without DS (*N* = 49)	102.3 (13.9)

				Male %: 100 μ_{age} ± σ: 41.4 ± 8.3 years	12.8 (3.6) 12.8 (11.5) 0.73 (1.25)
		DS (*N* = 67) Male %: 0 μ_{age} ± σ: 37.1 ± 12.7 years	122.5 (24.4) 13.4 (6.4) 15.4 (11.2) 0.21 (0.24)	Normal controls (*N* = 51) Male %: 0 μ_{age} ± σ: 39.9 ± 22.9 years	141.2 (36.3) 35.5 (34.6) 20.3 (10.2) 2.1 (1.52)
				Patients without DS (*N* = 20) Male %: 0 μ_{age} ± σ: 53.7 ± 16.6 years	134.4 (36.7) 11.9 (2.5) 3.7 (1.8) 0.44 (0.46)