|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author** | **Study Design** | **Population** | **Diagnosis of Alzheimer Disease** | **Matrix** | **Mean Metals Concentrations** | **Results** | **Adjustment Factors** | **Quality Assessment (Score)** |
| [13] | Case-control post-mortem | N=31(16 AD, 15 non AD) | BRAAK | Brain tissue: Frontal Cortex (FC) and Ventricular Fluid (VF) | [As] 145 ng/g FC (AD); 159 ng/g FC (non AD)[As] 18 ng/mL VF (AD);13 ng/mL VF (non AD) | Significantly lower [As] in frontal cortex (N.R.; p=0.033) and in ventricular fluid (N.R.; p=0.044) of AD subjects  | N.A. | 4 out of 12 |
| [14] | Case-control | N=207(89 AD, 118 non AD) | NINCDS-ADRDA | Serum | [As] 28.08µg/L (AD); 28.66µg/L (non AD) | No significant difference in [As] among AD and non AD subjects (N.R.; p=0.309) | Age | 6 out of 12 |
| [15] | Case-control | N=85(44 AD,41 non AD) | NINCDS-ADRDA | Serum | [As]35.7 nmol/L(AD); 38.7 nmol/L(non AD) | No statistically significant variation. | AgeGender | 5 out of 12 |
| [16] | Case-control | N=118(34 AD, 20 MCI, 24 SMC, 40 non AD) | NINCDS-ADRDA | Blood | [As] 3.55 µg/L (AD); 3.13 µg/L (non AD) | No statistically significant variation (F=1.204; p=0.312) | AgeSex Education | 6 out of 12 |

***Table 2. Summary results on Arsenic (As).*** *AD = Alzheimer Disease; Non-AD = Non Alzheimer Disease;NINCDS = National Institute of Neurological and Communicative Disorders and Stroke; ADRDA = Alzheimer’s Disease and Related Disorders Association; MCI= Mild cognitive impairment; SMC= subjective Memory Complaint; N.A.=Non Available; N.R.= Not Reported*

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author** | **Study Design** | **Population** | **Diagnosis of Alzheimer Disease** | **Matrix** | **Mean Metals Concentrations** | **Results** | **Adjustment Factors** | **Quality Assessment (Score)** |
| [13] | Case-control post-mortem | N=31(16 AD, 15 non AD) | BRAAK | Brain tissue: Frontal Cortex (FC) and Ventricular Fluid (VF) | [Cd] 20 ng/g in FC (AD); 30 ng/g in FC (non AD);[Cd] <LOQ in VF (AD);<LOQ in VF (non AD) | Significantly lower [Cd] is in AD than in non ADsubjects, in frontal cortex (N.R.; p=0.031) | N.A. | 4 out of 12 |
| [14] | Case-control | N=207(89AD, 118 non AD) | NINCDS-ADRDA | Serum | [Cd] 0.048µg/L (AD); 0.040µg/L (non AD) | No significant difference in [Cd] among AD and non AD subjects (N.R.; p=0.084) | Age | 6 out of 12 |
| [16] | Case-control | N=118(34 AD, 20 MCI, 24 SMC, 40 non AD) | NINCDS-ADRDA | Blood | [Cd] 0.03 µg/L (AD); 0.02 (non AD) | No statistically significant difference (N.R.; p=0.069) | AgeSex Education | 6 out of 12 |
| [17] | Case-Control | N=65(25 AD, 15 MCI, 25 non AD) | NINCDS-ADRDA | Serum | [Cd]= 0.0799µg/L (AD); 0.0640µg/L (non AD) | No statistically significant difference in [Cd] among AD and non ADsubjects. | N.A. | 5 out of 12 |
| [18] | Case-Control post-mortem | N= 45(18 AD, 11 DLB, 16 non AD) | BRAAK | Brain tissue(hippocampus, amygdala) | Hippocampus[Cd] 1.0 µM of wet tissue (AD); 0.7 µM of wet tissue (non AD)Amygdala[Cd] 1.0 µM of wet tissue (AD); 0.7 µM of wet tissue (non AD) | Statistically significant increase in amygdala [Cd] among AD and non-AD subjects (N.R.; p<0.05) | N.A. | 5 out of 12 |
| [19] | Case-control | N= 314(173 AD, 54 non AD, 87AD + vasc., ) | DSM-IV;NINCDS-ADRDA | PlasmaCSF | Plasma[Cd] 0,05 µg/L (AD);0.5 µg/L (AD+vasc);0.05 µg/L (non AD)CSF[Cd] <0.04 µg/L (AD subjects);<0.4 µg/L (AD+vasc)<0.04 µg/L (non AD) | No significant difference in [Cd] among AD and non ADsubjects | Age | 5 out of 12 |
| [20] | Case-control | N= 122(62 AD, 60 non AD) | NINCDS-ADRDA | NailHair | Nail[Cd] 0.39 µg/g (AD); 0.73 µg/g (non AD)Hair[Cd] 0.21 µg/g (AD); 0.31 µg/g (non AD) | Statistically significant difference in [Cd] (N.R.; p < 0.001) in AD subjects nailsStatistically significant lower [Cd]( N.R.; p < 0.01) in AD subjects hair | N.A. | 7 out of 12 |
| [21] | Case-control | N= 39(24 AD, 15 non AD) | NINCDS-ADRDA | Serum | [Cd] 0.0032 µg/dL(AD); 0.0011 µg/dL (non AD) | [Cd] in AD subjects were significantly higher (N.R.; p=0.001) | Age | 5 out of 12 |

***Table 3. Summary results on Cadmium (Cd).*** *AD = Alzheimer Disease; Non-AD = Non Alzheimer Disease; NINCDS = National Institute of Neurological and Communicative Disorders and Stroke; ADRDA = Alzheimer’s Disease and Related Disorders Association; MCI= Mild cognitive impairment; SMC= subjective Memory Complaint; N.A.=Non Available;LOQ = Limit of Quantification; CSF = Cerebrospinal Fluid; N.R.= Not Reported*

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author** | **Study Design** | **Population** | **Diagnosis of Alzheimer Disease** | **Matrix** | **Mean Metals Concentrations** | **Results** | **Adjustment Factors** | **Quality Assessment (Score)** |
| [13] | Case-control post-mortem | N=31(16 AD, 15 non AD) | BRAAK | Brain tissue: Frontal Cortex (FC) and Ventricular Fluid (VF) | FC[Cr] 154 ng/g [AD]; 91 ng/g (non AD)VF[Cr] 17.5 ng/ml [AD];14.4 ng/ml (non AD) | No statistically significant difference in among AD and non ADsubjects. | N.A. | 4 out of 12 |
| [15] | Case-control | N=85(44 AD,41 non AD) | NINCDS-ADRDA | Serum | [Cr] 22.7 nmol/L (AD); 17.2 nmol/L(non AD) | No statistically significant difference in among AD and non AD subjects. | AgeGender | 5 out of 12 |
| [16] | Case-control | N=118(34 AD, 20 MCI, 24 SMC,40 non AD) | NINCDS-ADRDA | Blood | [Cr]= 0.10 µg/L (AD); 0.21(non AD) | No statistically significant difference. | AgeSexEducation | 6 out 12 |
| [17] | Case-Control | N=65(25 AD, 15 MCI, 25 non AD) | NINCDS-ADRDA | Serum | [Cr] 0.207µg/L (AD);0.212µg/L (non AD) | No statistically significant difference in among AD and non ADsubjects. | N.A. | 5 out of 12 |
| [18] | Case-Control post-mortem | N= 45(18 AD, 11 DLB, 16 non AD) | BRAAK | Brain tissue(hippocampus, amygdala) | Hippocampus [Cr] 0.2 µM of wet tissue (AD);0.3 µM of wet tissue (non AD)Amygdala [Cr] 0.7µM of wet tissue (AD); 0.4 µM of wet tissue (non AD) | No statistically significant difference in among AD and non AD subjects. | N.A. | 5 out of 12 |

***Table 4. Summary results on Chrome (Cr).*** *AD = Alzheimer Disease; Non-AD = Non Alzheimer Disease; NINCDS = National Institute of Neurological and Communicative Disorders and Stroke; ADRDA = Alzheimer’s Disease and Related Disorders Association; MCI= Mild cognitive impairment; SMC= subjective Memory Complaint; N.A.=Non Available; CSF = Cerebrospinal Fluid; DLB= Dementia with Lewy bodies.; N.R.= Not Reported*

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author** | **Study Design** | **Population** | **Diagnosis of Alzheimer Disease** | **Matrix** | **MeanMetalsConcentrations** | **Results** | **Adjustment Factors** | **Quality Assessment (Score)** |
| [16] | Case-control | N=118 (34 AD, 20 MCI, 24 SMC, 40 non AD) | NINCDS-ADRDA | Blood | [Co]= 0.39 µg/L (AD); 0.39 (non AD) | No statistically significant variation (F=0.614; p=0.607) | AgeSexEducation | 6 out of 12 |
| [19] | Case-control | N= 314(173 AD, 54 non AD, 87AD + vasc., ) | DSM-IV;NINCDS-ADRDA | PlasmaCSF | Plasma[Co] 0.87 µg/L(AD); 0.80 µg/L(AD+vasc); 1.1 µg/L(non AD)CSF[Co] 0.08 µg/L(AD); 0.07 µg/L(AD+vasc); 0.08 µg/L(non AD) | No statistically significant variation | N.A. | 5 out of 12 |
| [20] | Case-control | N= 122(62 AD, 60 non AD) | NINCDS-ADRDA | NailHair | Nail[Co] 0.50 µg/g (AD); 0.62 µg/g (non AD)Hair[Co] 0.28 µg/g (AD); 0.41 µg/g (non AD) | AD subjects showed statistically significant lower [Co] (N.R.; p < 0.001) in hair | N.A. | 7 out of 12 |
| [22] | Case-control | N=177(53 AD, 124 non AD) | NINCDS-ADRDA | Serum | [Co] 0.11 µg/L (AD); 0.16 µg/L (non AD) | Statistically significant decrease in [Co] in AD subjects | AgeGenderDrug intake | 5 out of 12 |
| [23] | Case-control | N=318(264 AD, 54 non AD) | NINCDS-ADRDA | CSF | [Co] 0.08 µg/L (AD); 0.07 µg/L (ADMV); [Co] 0.08 µg/L (non AD) | No statistically significant variation. | N.A. | 5 out of 12 |

***Table 5. Summary results on* Cobalt (Co).** *AD = Alzheimer Disease; Non-AD = Non Alzheimer Disease; NINCDS = National Institute of Neurological and Communicative Disorders and Stroke; ADRDA = Alzheimer’s Disease and Related Disorders Association; MCI= Mild cognitive impairment; SMC= subjective Memory Complaint; N.A.=Non Available; CSF = Cerebrospinal Fluid; DSMIV-TR= Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition, Text Revision); N.R.= Not Reported*

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author** | **Study Design** | **Population** | **Diagnosis of Alzheimer Disease** | **Matrix** | **Mean Metals Concentrations** | **Results** | **Adjustment Factors** | **Quality Assessment (Score)** |
| [6] | Case-control post mortem | N=68(42 AD: 14 Moderate and 28 Severe;26 non AD) | BRAAK | Brain tissue (neocortex, Brodmann area 7) | [Cu] 20.7 mg/Kg(Moderate AD); 17.9 mg/Kg(Severe AD); 22.5 mg/Kg(non AD) | [Cu] is significantly decreased in severe AD subjects (N.R.; p<0.001). | N.A. | 5 out of 12 |
| [13] | Case-control post-mortem | N=31(16AD, 15 non AD) | BRAAK | Brain tissue: Frontal Cortex (FC) and Ventricular Fluid (VF) | [Cu]2112 ng/gFC (AD);2398 ng/gFC (Non AD)[Cu]117.5 ng/mLVF (AD);104.2 ng/mLVF (Non AD) | No statistically significant variation. | N.A. | 4 out of 12 |
| [15] | Case-control | N=85(44 AD,41 non AD) | NINCDS-ADRDA | Serum | [Cu] 16.2 nmol/L(AD); 15.3 nmol/L(non AD) | No statisticall significant variations. | AgeSex | 5 out of 12 |
| [16] | Case-control | N=118(34 AD, 20 MCI, 24 SMC, 40 non AD) | NINCDS-ADRDA | Blood | [Cu] 815.75 µg/L (AD); 703.88 (non AD) | [Cu] is increased in AD subjects (F=3.013; p=0.033) | AgeSex Education | 6 out 12 |
| [17] | Case-Control | N=65(25 AD, 15 MCI, 25 non AD) | NINCDS-ADRDA | Serum | [Cu] 1.126.8µg/L (AD); 1.058.5µg/L (non AD) | No statistically significant variation in [Cu] between AD and non AD subjects. | N.A. | 5 out of 12 |
| [18] | Case-Control post-mortem | N= 45(18 AD, 11 DLB, 16 non AD) | BRAAK | Brain tissue(hippocampus, amygdala) | AD[Cu] Hippocampus= 29.5 µM of wet tissue; [Cu] Amygdala= 27.8 µM of wet tissueNon AD[Cu] Hippocampus=57.7 µM of wet tissue;[Cu] Amygdala= 53.2 µM of wet tissue | Statistically significant [Cu] reduction in AD subjects (N.R.; p<0.01 both for Hippocampus and Amygdala). | N.A. | 5 out of 12 |
| [19] | Case-control | N= 314(173 AD, 54 non AD, 87AD + vasc., ) | DSM-IV;NINCDS-ADRDA | PlasmaCSF | Plasma[Cu] 1.2 mg/L (AD), 1.2 mg/L(AD + vasc) 1.2 mg/L (non AD)CSF[Cu] 18 mg/L (AD), 18 mg/L(AD + vasc) 18 mg/L (non AD) | No statistically significant variation. | Age | 5 out of 12 |
| [20] | Case-control | N= 122(62 AD, 60 non AD) | NINCDS-ADRDA | NailHair | Nail[Cu]14.63 µg/g (AD)40.04 µg/g (non AD)Hair[Cu]17.62 µg/g (AD),22.83 µg/g (non AD) | Statistically significant difference in [Cu] (N.R.; p < 0.001) in nail . in AD subjects.Statistically significant lower hair [Cu] (N.R.; p < 0.01) in AD subjects | N.A. | 7 out of 12 |
| [21] | Case-control | N= 39(24 AD, 15 non AD) | NINCDS-ADRDA | Serum | [Cu] 1.097 µg/dL (AD),0.901 µg/dL (non AD) | No significant difference was found in [Cu] among AD and non AD subjects | N.A. | 5 out of 12 |
| [22] | Case-control | N=177(53 AD, 124 non AD) | NINCDS-ADRDA | Serum | [Cu]= 945 µg/L (AD); 951 µg/L (non AD) | No significant differences among AD and non AD subjects | AgeGender, Drugintake | 5 out of 12 |
| [23] | Case-control | N=318(264 AD, 54 non AD) | NINCDS-ADRDA | CSF | [Cu] 18 µg/L (AD); [Cu]=18 µg/L (ADMV); [Cu]=18 µg/L (non AD) | No significant differences among AD and non AD subjects | N.A. | 5 out of 12 |
| [24] | Case-control | N=142(84 AD, 58 non AD) | NINCDS–ADRDA | Serum | [Cu] 15.46µmol/L (AD); 14.0µmol/L (non AD)[Non-Cp Cu] 2.1µmol/L (AD); 1.5µmol/L (non AD) | Significantly higher [Cu] (d=0.51;p=0.003) in AD subjects compared with healthy controls. | Age | 5 out of 12 |
| [25] | Case-control | N= 166(83 AD, 83 non AD) | NINCDS–ADRDADSM-IV-TR | Serum | [Cu] 121ug/dL (AD); 102 ug/dL (non AD) | [Cu] (t=-5.832; p < 0.001) is significantly increased copper concentration in AD subjects compared with non AD | N.A. | 4 out of 12 |
| [26] | Case-control | N= 89(15 AD, 41MS, 23 healthy controls and 10 healthy elderly controls) | NINCDS-ADRDA | Blood | [Cu] 73.27µg/L (AD); 609.7µg/L (healthy control); 631.6µg/L (healthy elderly control) | [Cu] is significantly decreased in AD subjects (F=1.212; p<0.001) | N.A. | 3 out of 12 |
| [27] | Case-control | N= 186(93 AD, 45 VaD, 48 non AD) | NINCDS-ADRDA | Serum | [Cu]15.82µmol/L (AD); 12.75µmol/L (non AD)[Free Cu]= 2.72µmol/L (AD); 0.24µmol/L (non AD) | Statistically significant decrease in [Cu] and [Free Cu] in AD subjects (F=6.708; p=0.002 and p<0.01 respectively) | N.A. | 6 out of 12 |
| [28] | Case-Control | N=50(25 AD, 25 non AD) | DSM IV-TRNINCDS-ADRDA | Serum | [Cu]1.1 mg/L (AD); 0.78 mg/L (non AD) | Statistically significant [Cu] higher in AD subjects (N.R.; p<0.001) | N.A. | 5 out of 12 |
| [29] | Case-Control post-mortem | N= 30(10 PD, 10 AD, 10 non AD) | NINCDS-ADRDA | Brain (temporal cortex) | [Cu]=4.86 ng/mg (AD); 4.05 ng/mg (non AD) | No statistically significant difference. | N.A. | 6 out of 12 |
| [30] | Case-control | N=87(36 AD, 18 MCI, 33 non AD) | NINCDS-ADRDA | Serum | [Cu] 1006.6 µg/L (AD); 878.8 µg/L (non AD) | [Cu] is significantly higher in AD subjects (p=0.038) | N.A. | 5 out of 12 |
| [31] | Case-Control | N= 108(52 ALS, 21 AD, 20 PD, 15 non AD) | DSM IV-TR | CSF | [Cu]= 17.4 ng/mL(Early-onset AD 10.3 ng/mL; Late-onset AD 20.9 ng/mL);[Cu]= 10.2 ng/mL (non AD) | CSF [Cu] is significantly higher (N.R.; p<0.05) in AD subjects. | N.A. | 4 out of 12 |
| [32] | Case-control | N=100(50 AD, 50 non AD) | NINCDS-ADRDA | Plasma | [Cu] M= 129.75 µg/dL[Cu]F= 132.78 µg/dL (AD)[Cu] M= 140.63 µg/dL[Cu]F= 145.29 µg/dL (non AD) | Statistically significant [Cu] decrease in plasma (F=3.97; p<0.01) in AD subjects | N.A. | 6 out of 12 |
| [33] | Case-control | N= 619(110 ADMAD:39;IAD36;SAD35.Fist-degree relativesAD (RAD)76; 87 PD.Fist-degree relatives PD (RPD) 46;87 VDFirst-degree relatives VD (RVD) 56; 134)Non AD55 Younger control (YCG) and 79 Elderly control (ECG) | NINCDS-ADRDA | Plasma | [Cu] 0.84 mg/L (AD) 0.79 mg/L (non AD) | [Cu] is significantly higher in patients with severe AD (N.R.; p<0.01) | N.A. | 6 out of 12 |
| [34] | Case-control | N=57(28 AD,29 non AD) | NINCDS-ADRDA | Serum | [Cu]=108 µg/dL(AD); 117 µg/dL(non AD)Free[Cu] 43.1% (AD); 38.5% (non AD) | [Cu] is significantly lower in AD patients (t=1.98; p=0.05) | N.A. | 6 out of 12 |
| [35] | Case-Control | N= 91(8 AD, 23 HD, 22 PD, 27 ALS11 non AD) | NINCDS-ADRDA | CSF | Free[Cu]=4 µg/L (AD)2.5 µg/L (non AD) | No significant difference in free Cu concentration between AD and non AD subjects. | N.A. | 6 out of 12 |
| [36] | Case-controlPost mortem | N= 23(3 Mild AD,8 Severe AD, 6 DLB, 6 non AD) | BRAAK | Brain tissue (Frontal cortex and hippocampus) | [Cu] 3.9 μg Cu/g (AD); 6.9 μg Cu/g (non AD) | [Cu] is decreased in severe AD close to the statistically significant threshold (N.R.; p=0.057) | Age | 5 out of 12 |
| [37] | Case-control | N= 104(51 AD,53 non AD) | NINCDS-ADRDA | Serum | [Cu] 16.1 µmol/L (AD), 13 µmol/L (non AD) | [Cu] is significantly higher (F=17.6; p<0.001) in AD subjects serum | AgeSex | 5 out of 12 |
| [38] | Case- Control | N=78(45 AD, 33 non AD) | NINCDS-ADRDA | HairSerum | Hair[Cu] 12.8µg/g (AD); 10.3 µg/g (non AD)Serum[Cu] 0.9µg/mL (AD); 1.01 µg/mL (non AD) | Hair [Cu] is increased (N.R.; p= 0.013 ) in AD subjects No significant difference was found in Serum [Cu] between AD and non AD subjects. | N.A. | 6 out of 12 |
| [39] | Case-control post mortem | N=18(9 AD, 9 non AD) | BRAAK | Brain tissue (cerebellum, motor cortex, sensory cortex, cingulate gyrus, temporal gyrus, entorhinal cortex, and hippocampus) | Brain-copper levels summed across all seven regions:[Cu]256 µM/dry Kg (AD), 406 µM/dry Kg (non AD) | [Cu] in AD subjects is significantly lower in every brain region: cerebellum (N.R.; p <0.0001); motor cortex (N.R.; p = 0.021); sensory cortex (N.R.; p= 0.027); cingulate gyrus (N.R.; p=0.0079); middle temporal gyrus (N.R.; p = 0.013); entorhinal cortex (N.R.; p= 0.0046); and hippocampus (N.R.; p= 0.070) | N.A. | 5 out of 12 |
| [40] | Case-control | N=702(399 AD and 303 non AD) | NINCDS–ADRDA | Serum | [Cu]14.98 µmol/L (AD); 13.05 µmol/L (Non-AD)[free Cu] 2.24 µmol/L (AD), 0.28µmol/L (non AD) | [Cu] and Free [Cu] is higher in AD subjects(N.R.; p<0.001) | Age | 6 out of 12 |
| [41] | CohortStudy | N= 957(186 AD, 76 MCI, 695 non AD) | NINCDS–ADRDA | Serum | [Cu] 13.52 µM (AD); 13.45 µM (non AD) | No significant differences among AD and non-AD subjects | N.A. | 9 out of 14 |
| [42] | Case-Control | N= 207(89 AD, 118 non AD) | NINCDS-ADRDA | Serum | [Cu] 1146.26 µg/L (AD); 1078.14µg/L(non AD)[Free Cu] 447.57 µg/L (AD); 428.19µg/L(non AD) | [Cu] is significantly higher in the AD subjects (N.R.; p = 0.026).Free [Cu] is not significantly different | AgeEducation | 7 out of 12 |
| [43] | Case-Control | N= 47(28 AD, 13 MCI, 6 non AD) | DSM-IV | Serum | [Cu] 1.01 mg/L (AD); 1.04 mg/L(non AD) | No significant differences among AD and non-AD subjects (t=0.587; p=0.560) | N.A. | 7 out of 12 |
| [44] | Case-control | N=104(50 AD, 24 VaD, 50 non AD) | NINCDS-ADRDA | Serum | [Cu] 156.2 µg/dL (AD); 134.46 µg/dL (non AD) | Statistically significant higher levels in [Cu] in AD subjects (F=6.52;p=0.002) | N.A. | 7 out of 12 |
| [45] | Case-control | N=152(72 AD, 80 non AD) | NINCDS-ADRDA | Serum | [Cu]=31.49 µmol/L (AD); 23.41 µmol/L (non AD) | No significant differences among AD and non AD subjects (t=1.494; p=0.138) | N.A. | 7 out of 12 |
| [46] | Case-control | N=57(30 AD, 27 non AD) | NINCDS-ADRDA | BloodBrain tissue (frontal cortex) | Blood[Cu] 270 µg/L (AD); 260 µg/L (non AD)Brain tissue[Cu] 1.45 µg/g (AD); 1.9 µg/g (non AD) | Brain [Cu] is significantly reduced in AD subjects (N.R.; p<0.0001)No significant difference was found in erythrocytes [Cu] between AD and non AD subjects. | N.A. | 3 out of 12 |
| [47] | Case-control | N=74(54 AD, 20 non AD) | NINCDS-ADRDA | Serum | [Cu] 15.1µmol/L (AD); 12.9µmol/L(non AD)Free [Cu] 2.1µmol/L (AD); 0.2 µmol/L (non AD) | Free [Cu] is significantly higher in AD subjects (N.R.; p=0.013)[Cu] is increased in AD subjects (N.R.; p=0.021) | N.A. | 5 out of 12 |
| [48] | Case-control | N=100(50 AD, 50 non AD) | NINCDS-ADRDA | Serum | [Cu] 137.8 mg/dl (AD); 132.5 mg/dl (non AD) | Copper levels were not significantly different between the study and the control populations. | Age | 4 out of 12 |

***Table 6.Summary results on Copper (Cu).****AD = Alzheimer Disease; Non-AD = Non Alzheimer Disease; NINCDS = National Institute of Neurological and Communicative Disorders and Stroke; ADRDA = Alzheimer’s Disease and Related Disorders Association; MCI= Mild cognitive impairment; SMC= subjective Memory Complaint; N.A.=Non Available; CSF = Cerebrospinal Fluid; DSMIV-TR= Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition, Text Revision);*non*CP= Ceruloplasmin; PD= Parkinson's disease; VaD = Vascular Dementia; d=Cohen’s d, standardized effect size for mean difference in the biochemical variables (d=0.2 small effect size; d=0.5 medium size; d=0.8 a large effect size; N.R.= Not Reported*

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author** | **Study Design** | **Population** | **Diagnosis of Alzheimer Disease** | **Matrix** | **MeanMetalsConcentrations** | **Results** | **AdjustmentFactors** | **QualityAssessment (Score)** |
| [6] | Case-control post mortem | N=68(42 AD: 14 Moderate and 28 Severe;26 non AD) | BRAAK | Brain tissue (neocortex, Brodmann area 7) | [Fe]= 360 mg/Kg(Moderate AD); 417mg/Kg(Severe AD); 374.8 mg/Kg(non AD) | [Fe] is significantly increased in severe AD subjects (N.R.; <0.001) | N.A. | 5 out of 12 |
| [13] | Case-control post-mortem | N=31(16AD, 15 non AD) | BRAAK | Brain tissue: Frontal Cortex (FC) and Ventricular Fluid (VF) | [Fe] 42571 ng/g FC (AD); 34140 ng/g FC (non AD)[Fe] 6994.9 ng/ml VF (AD); 1035.6 ng/ml VF (non AD) | [Fe] is significantly higher in AD subjects, but only in frontal cortex ( N.R.; p=0.018) | N.A. | 4 out of 12 |
| [15] | Case-control | N=85(44 AD, 41 non AD) | NINCDS-ADRDA | Serum | [Fe] 17,7 nmol/L(AD); 23,8 nmol/L(non AD) | Statistically significant decrease in [Fe] in AD subjects ( N.R.; p<0.05) | Age and sex. | 5 out of 12 |
| [16] | Case-control | N=118 (34 AD, 20 MCI, 24 SMC, 40 non AD) | NINCDS-ADRDA | Blood | [Fe]= 938.54 µg/L (AD); 1045.07 (non AD) | [Fe] in AD subjects were significantly lower(F=2.891; p=0.039) | AgeSexEducation | 6 out 12 |
| [17] | Case-Control | N=65(25 AD, 15 MCI, 25 non AD) | NINCDS-ADRDA | Serum | [Fe] 879.7µg/L (AD); 988.3µg/L (non AD) | No statistically significant difference | N.A. | 5 out of 12 |
| [18] | Case-Control post-mortem | N= 45(18 AD, 11 DLB, 16 non AD) | BRAAK | Brain tissue(hippocampus, amygdala) | [Fe] Hippocampus 697 µM of wet tissue (AD);Amygdala 955 µM of wet tissue (AD);[Fe] Hippocampus 669 µM of wet tissue (non AD);Amygdala694 µM of wet tissue (non AD) | Statistically significant increase in amygdala [Fe] in AD subjects (N.R.; p<0.05) | N.A. | 5 out of 12 |
| [19] | Case-control | N= 314(173 AD, 54 non AD, 87AD + vasc., ) | DSM-IV;NINCDS-ADRDA | PlasmaCSF | Plasma[Fe]1,6 mg/L (AD); 1.5 mg/L (AD+vasc); 1,8 mg/L(non AD)CSF[Fe]0.19 mg/L (AD); 0.17 mg/L (AD+vasc); 0.23 mg/L(non AD) | Non statistically significant variation | Age | 5 out of 12 |
| [20] | Case-control | N= 122(62 AD, 60 non AD) | NINCDS-ADRDA | NailHair | Nail[Fe]163.97 µg/g (AD), 384.62 µg/g (non AD)Hair[Fe] 229.31 (AD), 332.98 µg/g (non AD) | AD subject showed statistically significant difference in [Fe] (N.R.; p < 0.001) nail concentrations.AD subjects showed statistically significant lower concentrations of [Fe] ( N.R.; p = 0.001) in hair | N.A | 7 out of 12 |
| [21] | Case-control | N= 39(24 AD, 15 non AD) | NINCDS-ADRDA | Serum | [Fe]1.717 (AD), 0.651 µg/dL (non AD) | [Fe] in AD subjects were significantly higher ( N.R.; p=0.001) | N.A | 5 out of 12 |
| [22] | Case-control | N=177(53 AD, 124 non AD) | NINCDS-ADRDA | Serum | [Fe]= 858 µg/L (AD); 1.610 µg/L (non AD) | Statistically significant decrease in [Fe] in AD subjects ( N.R.; p<0.05) | AgeGenderDrugintake | 5 out of 12 |
| [23] | Case-control | N=318(264 AD, 54 non AD) | NINCDS-ADRDA | CSF | [Fe]=0.19 mg/L (AD);0.17 mg/L (ADMV); 0.23 mg/L (non AD) | No statistically significant variation | N.A. | 5 out of 12 |
| [24] | Case-control | N=142(84 AD, 58 non AD) | NINCDS–ADRDA | Serum | [Fe] 82.4 µg/dL (AD);80 µg/dL (non AD)[Transferrin] 2.5g/L (AD); 2.7g/L (non AD) | No statistically significant difference  | Age | 5 out of 12 |
| [25] | Case-control (Replication study) | N= 166(83 AD, 83 non AD) | NINCDS–ADRDA | Serum | [Fe] 119ug/dL (AD); 137ug/dL (non AD) | [Fe] (t=3.277; p < 0.05) concentration is significantly decreased in AD subjects | N.A. | 4 out of 12 |
| [27] | Case-control | N= 186 (93 AD, 45 VaD, 48 non AD) | NINCDS-ADRDA | Serum | [Fe] 72.77ng/dL (AD); 83.89 ng/dL (non AD)[Transferrin] 2.50g/L (AD); 2.71g/L (non AD) | No statistically significant difference | N.A. | 6 out of 12 |
| [29] | Case-Control post-mortem | N= 30(10 PD, 10 AD, 10 non AD) | NINCDS-ADRDA | Brain (temporalcortex) | [Fe] 123.07 ng/mg (AD); 131.25 ng/mg (non AD) | No statistically significant difference | N.A. | 6 out of 12 |
| [31] | Case-Control | N= 108(52 ALS, 21 AD, 20 PD,15 non AD) | DSM IV-TR | CSF | [Fe] 238.6 ng/mL(Early-onset AD 221.6 ng/mL; Late-onset AD 247.2 ng/mL)[Fe] 238.0 ng/mL (non AD) | No statistically significant variation | N.A. | 4 out of 12 |
| [32] | Case-control | N=100(50 AD, 50 non AD) | NINCDS-ADRDA | Plasma | [Fe] M=70.33 µg/dL[Fe]F= 64.52µg/dL (AD)[Fe] M=83.83µg/dL[Fe]F=79.15 µg/dL (Non-AD) | Statistically significant decrease in [Fe] (F=2.6; p<0.01) in AD subjects | N.A. | 6 out of 12 |
| [37] | Case-control | N= 104(51 AD,53 non AD) | NINCDS-ADRDA | Serum | [Fe] 73 µg/dL (AD), 85 µg/dL (non AD) | No statistically significant variation  | AgeSex | 5 out of 12 |
| [43] | Case-Control | N= 47(28 AD, 19 non AD) | DSM-IV-TR | Serum | [Fe]= 1.06 mg/L (AD); 1.14 mg/L(non AD) | No statistically significant variation | N.A. | 5 out of 12 |
| [45] | Case-control | N=152(72 AD, 80 non AD) | NINCDS-ADRDA | Serum | [Fe]=558 µg/dL (AD); [Fe]=610 µg/dL (non AD) | No statistically significant difference in [Fe] in AD subjects  | N.A. | 7 out of 12 |
| [49] | Case-control | N=70(34 AD, 36 non AD) | NINCDS-ADRDA | Plasma | [Ferritin]=187.4 g/L (AD); 153.9 g/L (non AD) | A statistically significant increase in [Fe] ( N.R.; p<0.001) in AD subjects | N.A. | 4 out of 12 |
| [50] | Community-based, cross-sectional cohort | N=1112(211 AD, 133 MCI, 768 non AD) | NINCDS-ADRDA | Blood | [Fe] 20.76 μmol/L (AD); 21.93 μmol/L (non AD)[Transferrin] 33.16 μmol/L (AD); 32.96 μmol/L (non AD)[Ferritin]114.40 μg/L (AD); 120.25 μg/L (non AD)TransferrinSaturation 25.66% (AD); 27.02% (non AD) | No statistically significant difference | AgeGenderAPOE-ε4 | 5 out of 12 |
| [51] | Case-Control | N= 159(107 AD, 52 non AD) | NINCDS-ADRDA | Serum | [Fe]83.2 µg/dL (AD); 87.1 µg/dL (non AD) | [Fe] in AD subjects is statistically significant lower (N.R.; p=0.001) | N.A. | 4 out of 12 |
| [52] | Case-control | N= 82(41 AD, 41 non AD) | NINCS-ADRDA | Serum | [Fe] 15 µmol/L (AD);18 µmol/L ( non AD) | No statistically significant variation. | AgeGender | 4 out of 12 |
| [53] | Case-control | N=95(49 AD, 46 non AD) | NINCDS-ADRDA | Serum | [Fe] 69.3 ng/dL (AD); 76.7 ng/dL (non AD) | No statistically significant difference in [Fe] between AD and non-AD subjects. | AgeSex | 6 out of 12 |

***Table 7. Summary results on Iron (Fe).*** *AD = Alzheimer Disease; Non-AD = Non Alzheimer Disease; NINCDS = National Institute of Neurological and Communicative Disorders and Stroke; ADRDA = Alzheimer’s Disease and Related Disorders Association; MCI= Mild cognitive impairment; SMC= subjective Memory Complaint; N.A.= Non Available; CSF = Cerebrospinal Fluid; DSMIV-TR= Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition, Text Revision); PD= Parkinson's disease; VaD = Vascular Dementia; M=Male; F=Female; ALS= Amyotrophic Lateral Sclerosis; d=Cohen’s d, standardized effect size for mean difference in the biochemical variables (d=0.2 small effect size; d=0.5 medium size; d=0.8 a large effect size; N.R.= Not Reported*

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author** | **Study Design** | **Population** | **Criteria for Diagnosis of Alzheimer Disease** | **Matrix** | **Mean Metals Concentrations** | **Results** | **AdjustmentFactors** | **QualityAssessment (Score)** |
| [13] | Case-control post-mortem | N=31(16 AD,15 non AD) | BRAAK | Brain tissue: Frontal Cortex (FC) and Ventricular Fluid (VF) | [Pb] 27 ng/g FC (AD); 27 ng/g FC (non AD)[Pb] 34 ng/ml VF (AD); 27.5 ng/ml VF (non AD) | No statistically significant variations. | N.A. | 4 out of 12 |
| [14] | Case-control | N=207(89 AD, 118 non AD) | NINCDS-ADRDA | Serum | [Pb]1.52µg/L (AD); 1.96µg/L (non AD) | No significant difference. | Age | 6 out of 12 |
| [16] | Case-control | N=118(34 AD, 20 MCI, 24 SMC, 40 non AD) | NINCDS-ADRDA | Blood | [Pb] 0.13 µg/L (AD); 0.16 (non AD) | No statistically significant variations(F=1.026;p=0.384) | AgeSexEducation | 6 out of 12 |
| [19] | Case-control | N= 314(173 AD, 54 non AD, 87AD + vasc., ) | DSM-IV;NINCDS-ADRDA | PlasmaCSF | Plasma[Pb] 0.72 µg/L (AD); 0.59 µg/L (AD+vasc); 0.61 µg/L (non AD)CSF[Pb] 0.23 µg/L(AD); 0.24 µg/L (AD+vasc)0.32 µg/L (non AD) | In CSF [Pb] is significantly lower in AD subjects (N.R.; p ≤0.010) | N.A. | 5 out of 12 |
| [22] | Case-control | N=177(53 AD, 124 non AD) | NINCDS-ADRDA | Serum | [Pb]= 0.38 µg/L (AD); 0.53 µg/L (non AD) | No statistically significant variations. | AgeGenderDrugintake | 5 out of 12 |
| [23] | Case-control | N=318(264 AD, 54 non AD) | NINCDS-ADRDA | CSF | [Pb] 0.23 µg/L (AD); 0.24 µg/L (ADMV); [Pb] 0.32 µg/L (non AD) | No statistically significant variations | N.A. | 5 out of 12 |
| [26] | Case-control | N= 89(15 AD, 41MS, 23 healthy controls and 10 healthy elderly controls) | NINCDS-ADRDA | Blood | [Pb] 14.04µg/L (AD); 23.15µg/L (healthy control); 24.60µg/L (healthy elderly control) | [Pb] is decreased in AD subjects (F=1.482; p<0.001) | N.A. | 3 out of12 |
| [54] | Case-control | N=210(80 AD, 130 non AD) | NINCDS-ADRDA | BloodSerum | Blood[Pb] 1.90 µg/dL (AD); 2.19 µg/dL (non AD)Serum[Pb] 0.20 µg/dL (AD); 0.17 µg/dL (non AD) | Statistically significant difference in blood [Pb] (N.R.; p=0.035) in AD subjects | N.A. | 4 out of 12 |

***Table 8. Summary results on* Lead (Pb).***AD = Alzheimer Disease; Non-AD = Non Alzheimer Disease; NINCDS = National Institute of Neurological and Communicative Disorders and Stroke; ADRDA = Alzheimer’s Disease and Related Disorders Association; MCI= Mild cognitive impairment; SMC= subjective Memory Complaint; N.A.=Non Available; CSF = Cerebrospinal Fluid; DSMIV-TR= Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition, Text Revision); PD= Parkinson's disease.*

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author** | **Study Design** | **Population** | **Diagnosis of Alzheimer Disease** | **Matrix** | **Mean MetalsConcentrations** | **Results** | **AdjustmentFactors** | **QualityAssessment (Score)** |
| [13] | Case-control post-mortem | N=31(16 AD,15 non AD) | BRAAK | Brain tissue: Frontal Cortex (FC) and Ventricular Fluid (VF) | [Mn] 151 ng/g FC (AD); 182 ng/g; FC (non AD)[Mn] 25.1 ng/ml VF (AD); 23.5 ng/ml VF (non AD) | No statistically significant variations. | N.A. | 4 out of 12 |
| [15] | Case-control | N=85(44 AD,41 non AD) | NINCDS-ADRDA | Serum | [Mn] 21.4 nmol/L(AD)13.3 nmol/L(non AD) | No statistically significant variations | AgeSex | 5 out of 12 |
| [16] | Case-control | N=118(34 AD, 20 MCI, 24 SMC, 40 non AD) | NINCDS-ADRDA | Blood | [Mn]= 0.59 µg/L (AD); 1.24 (non AD) | [Mn] in AD subjects were significantly lower(F=14.783; p<0.001) | AgeSexEducation | 6 out 12 |
| [17] | Case-Control | N=65(25 AD, 15 MCI, 25 healthy control) | NINCDS-ADRDA | Serum | [Mn] 0.665µg/L (AD);1.09µg/L (non AD) | In AD subjects total serum [Mn] is significantly reduced (N.R.; p<0.05) | N.A. | 5 out of 12 |
| [18] | Case-Control post-mortem | N= 45(18 AD, 11 DLB, 16 non AD) | BRAAK | Brain tissue(hippocampus, amygdala) | AD[Mn] Hippocampus= 7.4µM of wet tissue[Mn] Amygdala= 8.8 µM of wet tissueNon AD[Mn] Hippocampus= 8.7µM of wet tissue[Mn] Amygdala= 7.8µM of wet tissue | No statistically significant variations. | N.A. | 5 out of 12 |
| [19] | Case-control | N= 314(173 AD, 54 non AD, 87AD + vasc., ) | DSM-IV;NINCDS-ADRDA | PlasmaCSF | Plasma[Mn] 1.5 µg/L(AD); 1.4 µg/L(AD+vasc); 0.94 µg/L(non AD)CSF[Mn] 0.61 µg/L(AD); 0.63 µg/L(AD+vasc); 0.73 µg/L(non AD) | Plasma [Mn] is significantly higher in AD subjects (N.R.; p ≤0.001)CSF [Mn] is significantly lower in AD subjects (N.R.; p ≤0.010) | N.A | 5 out of 12 |
| [20] | Case-control | N= 122(62 AD, 60 non AD) | NINCDS-ADRDA | NailHair | Nail[Mn] 2.09 µg/g (AD); 6.76 µg/g (non AD)Hair[Mn] 0.49 µg/g (AD);1.15 µg/g (AD) | Statistically significant difference in nail [Mn] (N.R.; p < 0.001)AD subjects showed statistically significant lower [Mn] (N.R.; p = 0.001) in hair | N.A | 7 out of 12 |
| [21] | Case-control | N= 39(24 AD, 15 non AD) | NINCDS-ADRDA | Serum | [Mn] 0.012 µg/dL (AD),0.089 µg/dL (non AD) | [Mn] is lower in AD subjects (N.R.; p=0.001) | N.A. | 5 out of 12 |
| [22] | Case-control | N=177(53 AD, 124 non AD) | NINCDS-ADRDA | Serum | [Mn] 0.60 µg/L (AD); 0.60 µg/L (non AD) | No statistically significant variations. | AgeGenderDrugintake | 5 out of 12 |
| [23] | Case-control | N=318(264 AD, 54 non AD) | NINCDS-ADRDA | CSF | [Mn] 0.61 µg/L (AD);0.63 µg/L (ADMV); 0.73 µg/L (non AD) | Statistically significant difference in [Mn] in AD subjects (N.R.; p=0.004) and in ADMV subjects (N.R.; p=0.048) | N.A. | 5 out of 12 |
| [29] | Case-Control post-mortem | N= 30(10 PD, 10 AD, 10 non AD) | NINCDS-ADRDA | Brain (temporalcortex) | [Mn]=0.84 ng/mg (AD); 1.23 ng/mg (non AD) | No statistically significant difference. | N.A. | 5 out of 12 |
| [31] | Case-Control | N= 108(52 ALS, 21 AD, 20 PD, 15 non AD) | DSM IV-TR | CSF | [Mn] 1.8 ng/mL (AD);1.2 ng/mL (early-onset AD); 2.1 ng/mL (late-onset AD); 1.9 ng/mL (non AD) | No statistically significant variations. | N.A. | 4 out of 12 |

***Table 9. Summary results on* Manganese (Mn).** *AD = Alzheimer Disease; Non-AD = Non Alzheimer Disease; NINCDS = National Institute of Neurological and Communicative Disorders and Stroke; ADRDA = Alzheimer’s Disease and Related Disorders Association; MCI= Mild cognitive impairment; SMC= subjective Memory Complaint; N.A.= Non Available; CSF = Cerebrospinal Fluid; DSMIV-TR= Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition, Text Revision); PD= Parkinson's disease; VaD = Vascular Dementia; ALS= Amyotrophic Lateral Sclerosis; DLB= Dementia with Lewy bodies.*

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author** | **Study Design** | **Population** | **Diagnosis of Alzheimer Disease** | **Matrix** | **Mean MetalsConcentrations** | **Results** | **AdjustmentFactors** | **QualityAssessment (Score)** |
| [13] | Case-control post-mortem | N=31(16 AD,15 non AD) | BRAAK | Brain tissue: Frontal Cortex (FC) and Ventricular Fluid (VF) | [Hg]10 ng/g FC (AD); 9 ng/g FC (non AD)[Hg]<LOQ VF(AD); <LOQ VF (non AD) | No statistically significant variation. | N.A. | 4 out of 12 |
| [14] | Case-control | N=207(89 AD, 118 non AD) | NINCDS-ADRDA | Serum | [Hg]= 1.46µg/L (AD);1.54µg/L (non AD) | No statistically significant difference | Age | 6 out of 12 |
| [16] | Case-control | N=118(34 AD, 20 MCI, 24 SMC, 40 non AD) | NINCDS-ADRDA | Blood | [Hg] 0.32 µg/L (AD); 0.62 (non AD) | [Hg] in AD subjects were significantly lower(F=8.732; p<0.001) | AgeSexEducation | 6 out 12 |
| [19] | Case-control | N= 314(173 AD, 54 non AD, 87AD + vasc., ) | DSM-IV;NINCDS-ADRDA | PlasmaCSF | Plasma[Hg] 0.28 (AD); 0.23 (AD+vasc);<0.21 µg/L(non AD)CSF[Hg] <0,21 µg/L(AD);<0.21 (AD+vasc);<0,21 µg/L (non AD) | [Hg] is significantly higher in subjects with AD (N.R.; p ≤0.001) | Age | 5 out of 12 |
| [20] | Case-control | N= 122(62 AD, 60 non AD) | NINCDS-ADRDA | NailHair | Nails[Hg]0.19 µg/g (AD);0.28 µg/g (non AD)Hair[Hg]0.12 µg/g (AD);0.19 µg/g (non AD) | AD subjects showed statistically significant difference [Hg] (N.R.; p < 0.001)AD subjects showed statistically significant lower [Hg] (N.R.; p < 0.01) in hair | N.A. | 7 out of 12 |
| [23] | Case-control | N=318(264 AD, 54 non AD) | NINCDS-ADRDA | CSF | AD[Hg]<0.21 µg/LADMV[Hg] <0.21 µg/LHC[Hg] <0.21 µg/L | No statisticallysignificantvariations. | N.A. | 5 out of 12 |
| [26] | Case-control | N= 89(15 AD, 41MS, 23 healthy controls and 10 healthy elderly controls) | NINCDS-ADRDA | Blood | [Hg] 5.415µg/L (AD); 6.111µg/L (healthy control); 3.326µg/L (healthy elderly control) | No statistically significant difference.(F=11.68; p=0.0008) | N.A. | 3 out of 12 |
| [54] | Case-control | N=210(80 AD, 130 non AD) | NINCDS-ADRDA | BloodSerum | Blood[Hg] 2.93 µg/g (AD);3.23 µg/g (non AD)Serum[Hg]1.45 µg/g (AD);1.43 µg/g (non AD) | No statistically significant variations. | N.A. | 4 out of 12 |

**Table 10. Summary results on Mercury (Hg).***AD = Alzheimer Disease; Non-AD = Non Alzheimer Disease; NINCDS = National Institute of Neurological and Communicative Disorders and Stroke; ADRDA = Alzheimer’s Disease and Related Disorders Association; MCI= Mild cognitive impairment; SMC= subjective Memory Complaint; N.A.=Non Available; CSF = Cerebrospinal Fluid; DSMIV-TR= Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition, Text Revision); PD= Parkinson's disease; LOQ = Limit of Quantification.*

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author** | **Study Design** | **Population** | **Diagnosis of Alzheimer Disease** | **Matrix** | **Mean MetalsConcentrations** | **Results** | **AdjustmentFactors** | **QualityAssessment (Score)** |
| [16] | Case-control | N=118 (34 AD, 20 MCI, 24 SMC, 40 non AD) | NINCDS-ADRDA | Blood | [Mo]= 1.20 µg/L (AD); 0.83 (non AD) | [Mo] is increased in AD subjects (F=4.199; p=0.008) | AgeSexEducation | 6 out of 12 |
| [17] | Case-Control | N=65(25 AD, 15 MCI, 25 non AD) | NINCDS-ADRDA | Serum | [Mo] 1.02µg/L (AD); 1.06µg/L (non AD) | No statistically significant differences. | N.A. | 5 out of 12 |
| [19] | Case-control | N= 314(173 AD, 54 non AD, 87AD + vasc., ) | DSM-IV;NINCDS-ADRDA | PlasmaCSF | Plasma[Mo] 1 µg/L(AD);1.1 µg/L(AD+vasc); 1 µg/L(non AD)CSF[Mo] 0.23 µg/L(AD); 0.26 µg/L(AD+vasc); 0.24 µg/L(non AD) | No statistically significant variation. | N.A. | 5 out of 12 |

***Table 11. Summary results on* Molybdenum (Mo).** *AD = Alzheimer Disease; Non-AD = Non Alzheimer Disease; NINCDS = National Institute of Neurological and Communicative Disorders and Stroke; ADRDA = Alzheimer’s Disease and Related Disorders Association; MCI= Mild cognitive impairment; SMC= subjective Memory Complaint; N.A.=Non Available; CSF = Cerebrospinal Fluid; DSMIV-TR= Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition, Text Revision).*

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author** | **Study Design** | **Population** | **Diagnosis of Alzheimer Disease** | **Matrix** | **MeanMetalsConcentrations** | **Results** | **AdjustmentFactors** | **QualityAssessment (Score)** |
| [13] | Case-control post-mortem | N=31(16 AD,15 non AD) | BRAAK | Brain tissue: Frontal Cortex (FC) and Ventricular Fluid (VF) | [Ni] 52 ng/g FC (AD); 36 ng/g FC (non AD)[Ni] 19.6 ng/ml VF (AD); 12 ng/ml VF (non AD) | No statistically significant variations.  | N.A. | 4 out of 12 |
| [16] | Case-control | N=118(34 AD, 20 MCI, 24 SMC, 40 non AD) | NINCDS-ADRDA | Blood | [Ni] 1.10 µg/L (AD); 1.08 (non AD) | No statistically significant variations. | AgeSexEducation | 6 out 12 |
| [19] | Case-control | N= 314(173 AD, 54 non AD, 87AD + vasc., ) | DSM-IV;NINCDS-ADRDA | PlasmaCSF | Plasma[Ni] 2.9 µg/L (AD);2.8 µg/L (AD+vasc);2,8 µg/L(non AD)CSF[Ni] 0.36 µg/L (AD); 0.43 µg/L (AD+vasc); <0.28 µg/L(non AD) | No statistically significant variations. | N.A. | 5 out of 12 |
| [22] | Case-control | N=177(53 AD, 124 non AD) | NINCDS-ADRDA | Serum | [Ni] 0.53 µg/L (AD); 0.39 µg/L (non AD) | No statistically significant variations. | AgeGenderDrug intake | 5 out of 12 |
| [23] | Case-control | N=318(264 AD, 54 non AD) | NINCDS-ADRDA | CSF | [Ni] 0.36 µg/L (AD); 0.43 µg/L (ADMV);<0.28 µg/L (non AD) | No statistically significant variations. | N.A. | 5 out of 12 |
| [29] | Case-Control post-mortem | N= 30(10 PD, 10 AD, 10 non AD) | NINCDS-ADRDA | Brain (temporalcortex) | [Ni] 1.09 ng/mg (AD); 1.51 ng/mg (non AD) | No statistically significant difference. | N.A. | 5 out of 12 |

***Table 12. Summary results on* Nickel (Ni). *AD = Alzheimer Disease; Non-AD = Non Alzheimer Disease; NINCDS = National Institute of Neurological and Communicative Disorders and Stroke; ADRDA = Alzheimer’s Disease and Related Disorders Association; MCI= Mild cognitive impairment; SMC= subjective Memory Complaint; N.A.=Non Available; CSF = Cerebrospinal Fluid; DSMIV-TR= Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition, Text Revision); PD= Parkinson's disease.***

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author** | **Study Design** | **Population** | **Diagnosis of Alzheimer Disease** | **Matrix** | **MeanMetalsConcentrations** | **Results** | **AdjustmentFactors** | **QualityAssessment (Score)** |
| [15] | Case-control | N=85(44 AD,41 non AD) | NINCDS-ADRDA | Serum | [Se]1.42 nmol/L(AD); 1.39 nmol/L(non AD) | No statistically significant variation. | AgeSex | 5 out of 12 |
| [16] | Case-control | N=118 (34 AD, 20 MCI, 24 SMC, 40 non AD) | NINCDS-ADRDA | Blood | [Se]= 70.36 µg/L (AD); 82.62 (non AD) | [Se] is decreased in AD subjects (F=3.199; p=0.026) | AgeSexEducation | 6 out of 12 |
| [17] | Case-Control | N=65(25 AD, 15 MCI, 25 non AD) | NINCDS-ADRDA | Serum | [Se] 120.5µg/L (AD); 122.9µg/L (non AD) | No statistically significant variation. | N.A. | 5 out of 12 |
| [23] | Case-control | N=318(264 AD, 54 non AD) | NINCDS-ADRDA | CSF | [Se]1.8 µg/L (AD);1.8 µg/L (ADMV);1.9 µg/L (non AD) | No statistically significant variation. | N.A. | 5 out of 12 |
| [26] | Case-control | N= 89(15 AD, 41MS, 23 healthy controls and 10 healthy elderly controls) | NINCDS-ADRDA | Blood | [Se] 42.78µg/L (AD); 71.10µg/L (healthy control); 73.27µg/L (healthy elderly control) | [Se] is decreased in AD subjects (F=2.301; p<0.001) | N.A. | 3 out of 12 |
| [32] | Case-control | N=100(50 AD, 50 non AD) | NINCDS-ADRDA | Plasma | [Se]M= 58.15µg/dl[Se]F= 58.43 µg/dl (AD)[Se]M=67.84 µg/dl[Se]F= 68.70 µg/dl (non AD) | Statistically significant decrease [Se] (F=6.77; p<0.001) in AD subjects | N.A | 6 out of 12 |

***Table 13. Summary results on S*elenium (Se).** *AD = Alzheimer Disease; Non-AD = Non Alzheimer Disease; NINCDS = National Institute of Neurological and Communicative Disorders and Stroke; ADRDA = Alzheimer’s Disease and Related Disorders Association; MCI= Mild cognitive impairment; SMC= subjective Memory Complaint; N.A.=Non Available; CSF = Cerebrospinal Fluid; DSMIV-TR= Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition, Text Revision); M=Male; F=Female; MS= Multiple Sclerosis; DLB= Dementia with Lewy bodies.*

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author** | **Study Design** | **Population** | **Diagnosis of Alzheimer Disease** | **Matrix** | **Mean MetalsConcentrations** | **Results** | **AdjustmentFactors** | **QualityAssessment (Score)** |
| [13] | Case-control post-mortem | N=31(16 AD,15 non AD) | BRAAK | Brain tissue: Frontal Cortex (FC) and Ventricular Fluid (VF) | [Sn] 26 ng/g FC (AD); 32 ng/g FC (non AD)[Sn]7 ng/ml VF (AD): 5 ng/ml VF non AD) | No statistically significant variations. | N.A. | 4 out of 12 |
| [16] | Case-control | N=118 (34 AD, 20 MCI, 24 SMC, 40 non AD) | NINCDS-ADRDA | Blood | [Sn] 0.22 µg/L (AD); 0.14 (non AD) | No statistically significant variations (F=0.380; p=0.768) | AgeSexEducation | 6 out 12 |
| [19] | Case-control | N= 314(173 AD, 54 non AD, 87AD + vasc., ) | DSM-IV;NINCDS-ADRDA | PlasmaCSF | Plasma[Sn] 0.9 µg/L(AD); 0.81 µg/L (AD+vasc); 0.85 µg/L(non AD)CSF[Sn] 0.21µg/L(AD); 0.16 µg/L (AD+vasc); 0.25 µg/L(non AD) | No statistically significant variations. | N.A. | 5 out of 12 |
| [22] | Case-control | N=177(53 AD, 124 non AD) | NINCDS-ADRDA | Serum | [Sn] 1.18 µg/L (AD); 0.53 µg/L (non AD) | No statistically significant variations. | AgeGender, Drugintake | 5 out of 12 |

***Table 14.Summary results on* Tin (Sn).***AD = Alzheimer Disease; Non-AD = Non Alzheimer Disease; NINCDS = National Institute of Neurological and Communicative Disorders and Stroke; ADRDA = Alzheimer’s Disease and Related Disorders Association; MCI= Mild cognitive impairment; SMC= subjective Memory Complaint; N.A.=Non Available; CSF = Cerebrospinal Fluid; DSMIV-TR= Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition, Text Revision).*

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author** | **Study Design** | **Population** | **Diagnosis of Alzheimer Disease** | **Matrix** | **Mean MetalsConcentrations** | **Results** | **AdjustmentFactors** | **QualityAssessment (Score)** |
| [13] | Case-control post-mortem | N=31(16AD,15 non-AD) | BRAAK | Brain tissue: Frontal Cortex (FC) and Ventricular Fluid (VF) | [V] 3 ng/g FC (AD); 5 ng/g FC (Non-AD)[V] <LOQ VF (AD); <LOQ VF (Non-AD) | No statistically significant variations. | N.A. | 4 out of 12 |
| [16] | Case-control | N=118(34 AD, 20 MCI, 24 SMC,40 non AD) | NINCDS-ADRDA | Blood | [V]= 0.08 µg/L (AD); 0.04 (non AD) | [V] is increased in AD subjects (N.R.; p<0.001) | AgeSexEducation | 6 out 12 |
| [17] | Case-Control | N=65(25 AD, 15 MCI, 25 non AD) | NINCDS-ADRDA | Serum | [V] 0.0599µg/L (AD); 0.0598µg/L (non AD) | No statistically significant difference. | N.A. | 5 out of 12 |
| [19] | Case-control | N= 314(173 AD, 54 non AD, 87AD + vasc., ) | DSM-IV;NINCDS-ADRDA | PlasmaCSF | Plasma[V] <2.2 µg/L(AD);<2.2 µg/L(AD+vasc); <2.2 µg/L(non AD)CSF[V] 2.9 µg/L(AD); 2.9 µg/L(AD+vasc); 3.2 µg/L(non AD) | In CSF [V] is significantly lower in AD subjects (N.R.; p ≤0.010) | N.A. | 5 out of 12 |

***Table 15. Summary results on* Vanadium (V).** *AD = Alzheimer Disease; Non-AD = Non Alzheimer Disease; NINCDS = National Institute of Neurological and Communicative Disorders and Stroke; ADRDA = Alzheimer’s Disease and Related Disorders Association; MCI= Mild cognitive impairment; SMC= subjective Memory Complaint; N.A.=Non Available; CSF = Cerebrospinal Fluid; DSMIV-TR= Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition, Text Revision); LOQ = Limit of Quantification.*

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author** | **Study Design** | **Population** | **Diagnosis of Alzheimer Disease** | **Matrix** | **MeanMetalsConcentrations** | **Results** | **AdjustmentFactors** | **QualityAssessment (Score)** |
| [6] | Case-control post mortem | N=68(42 AD: 14 Moderate and 28 Severe;26 non AD) | BRAAK | Brain tissue (neocortex, Brodmann area 7) | [Zn] 42.5 mg/Kg(Moderate AD); 45.7 mg/Kg (Severe AD); 45.8 mg/Kg(non AD) | No significantly differences. | N.A. | 4 out of 12 |
| [13] | Case-control post-mortem | N=31(16 AD,15 non AD) | BRAAK | Brain tissue: Frontal Cortex (FC) and Ventricular Fluid (VF) | [Zn] 12099 ng/g FC (AD); 12073 ng/g FC (non AD)[Zn]=845.2 ng/ml VF (AD); 732.4 ng/ml VF (non AD) | No statistically significant variations. | N.A. | 4 out of 12 |
| [16] | Case-control | N=118 (34 AD, 20 MCI, 24 SMC, 40 non AD) | NINCDS-ADRDA | Blood | [Zn]= 609.40 µg/L (AD); 697.87 (non AD) | [Zn] is decreased in AD subjects (N.R.; p=0.020) | AgeSexEducation | 6 out of 12 |
| [17] | Case-Control | N=65(25 AD, 15 MCI, 25 non AD) | NINCDS-ADRDA | Serum | [Zn] 815 µg/L (AD); 910.5µg/L (non AD) | In AD subjects [Zn] is significantly reduced (N.R.; p<0.05) | N.A. | 5 out of 12 |
| [18] | Case-Control post-mortem | N= 45(18 AD, 11 DLB, 16 no AD) | BRAAK | Brain tissue(hippocampus, amygdala) | AD[Zn]Hippocampus= 293 µM of wet tissue[Zn]Amygdala= 273 µM of wet tissueNon AD[Zn] Hippocampus= 297 µM of wet tissue[Zn] Amygdala= 264 µM of wet tissue | No significantly differences. | N.A. | 5 out of 12 |
| [22] | Case-control | N=177(53 AD, 124 non AD) | NINCDS-ADRDA | Serum | [Zn] 691 µg/L (AD); 795 µg/L (non AD) | Statistically significant [Zn] increase in AD subjects (N.R.; p<0.05) | AgeGenderDrugintake | 5 out of 12 |
| [23] | Case-control | N=318 (264 AD, 54 non AD) | NINCDS-ADRDA | CSF | [Zn]17 µg/L (AD); 17 µg/L (ADMV); 17 µg/L (non AD) | No statistically significant variation. | N.A. | 5 out of 12 |
| [25] | Case-control | N= 166(83 AD, 83 non AD) | NINCDS–ADRDADSM-IV-TR | Serum | [Zn] 69ug/dl (AD); 72ug/dl (non AD) | No significantly differences. | N.A. | 4 out of 12 |
| [26] | Case-control | N= 89(15 AD, 41MS, 23 healthy controls and 10 healthy elderly controls) | NINCDS-ADRDA | Blood | [Zn] 1.788µg/L (AD); 2.810µg/L (healthy control); 3.080µg/L (healthy elderly control) | [Zn] is decreased in AD subjects (F=1.364; p<0.001). | N.A. | 3 out of 12 |
| [38] | Case- Control | N=78(45 AD, 33 non AD) | NINCDS-ADRDA | HairSerum | Hair[Zn] 75µg/g (AD);98 µg/g (non AD)Serum[Zn] 0.47µg/mL (AD); 0.52 µg/mL (non AD) | Statistically significant decrease in hair [Zn] in AD subjects (N.R.; p=0.02)No statistically significant difference in serum [Zn] | N.A. | 6 out of 12 |
| [43] | Case-Control | N= 47(28 AD, 19 non AD) | DSM-IV-TR | Serum | [Zn] 0.62 mg/L (AD); 0.69 mg/L(non AD) | [Zn] in AD group is significantly lower (t=2.086; p=0.043) | N.A. | 5 out of 12 |
| [45] | Case-control | N=152 (72 AD, 80 non AD) | NINCDS-ADRDA | Serum | [Zn]111.3 µg/dL (AD); 123 µg/dL (non AD) | No statistically significant differences(t=0.810; p=0.419) | N.A. | 7 out of 12 |
| [55] | Cross-sectional | N=958(205AD, 753 nonAD) | NINCDS-ADRDA | Serum | [Zn] 12.206 µM(AD); 12.730 µM(non AD) | Decreased [Zn] in AD is an effect of ageing. | AgeSexApoEε4 | 7 out of 14 |

***Table 16. Summary results on* Zinc (Zn).** *AD = Alzheimer Disease; Non-AD = Non Alzheimer Disease; NINCDS = National Institute of Neurological and Communicative Disorders and Stroke; ADRDA = Alzheimer’s Disease and Related Disorders Association; MCI= Mild cognitive impairment; SMC= subjective Memory Complaint; N.A.=Non Available; CSF = Cerebrospinal Fluid; DSMIV-TR= Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition, Text Revision); MS= Multiple Sclerosis; DLB= Dementia with Lewy bodies.*