**SUPPLEMENTAL METHODS AND DATA for** ***Serum Vitamin D Concentrations and Cognitive Change Over 20-Years: The Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS)***

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**Measurement of Cognition Methods**

The DWRT (1) is a test of recent memory and verbal learning. Participants learned 10 common nouns by using the word in sentences. After a five-minute delay, participants were given 1 minute to recall the words. The score is the total number of words recalled correctly.

The DSST (2) is a test of processing speed and executive function. Participants translated numbers to symbols using a key. The score ranges from 0 to 93 and is the number of numbers correctly translated to symbols within 1.5 minutes.

The WFT (3) is a test of language and executive function. Participants are asked to spontaneously say words starting with a letter, excluding proper places or names. Participants were given 1 minute for each of the following 3 letters: “F”, “A”, and “S”. The score is the total number of words produced over the three trials.

**References**

1. Knopman DS, Ryberg S**.** A verbal memory test with high predictive accuracy for dementia of the Alzheimer type. Arch Neurol. 1989;46(2):141-5.

2. Wechsler D**.** Wechsler Adult Intelligence Scale-Revised (WAIS-R) Manual. New York: Psychological Corp; 1987.

3. Benton AL, Hamsher K**.** Multilingual Aphasia Examination, 2nd Edition. Iowa City: AJA Associates; 1989.

Appendix Table 1. Number of Participants with Missing Data that was Imputed.

|  |  |
| --- | --- |
| Variable | Number of Participants with Missing Data that was Imputed |
| Global Z-Score (Baseline, Visit 2, 1990-1992) | 139 |
| Global Z-Score (Visit 4, 1996-1998) | 2378 |
| Global Z-Score (Visit 5, 2011-2013) | 7020 |
| Body Mass Index (Baseline, Visit 2, 1990-1992) | 16 |
| Physical Activity Index (Baseline, Visit 2, 1990-1992) | 44 |
| Smoking Status (Baseline, Visit 2, 1990-1992) | 6 |
| Total Cholesterol (Baseline, Visit 2, 1990-1992) | 24 |
| HDL Cholesterol (Baseline, Visit 2, 1990-1992) | 44 |
| Apolipoprotein ϵ4 Genotype (Baseline, Visit 2, 1990-1992) | 386 |
| Hypertension (Baseline, Visit 2, 1990-1992) | 32 |
| Cardiovascular Disease (Baseline, Visit 2, 1990-1992) | 250 |
| Parathyroid Hormone (Baseline, Visit 2, 1990-1992) | 132 |
| Calcium (Baseline, Visit 2, 1990-1992) | 134 |
| Phosphate (Baseline, Visit 2, 1990-1992) | 133 |

Appendix Table 2. Baseline Characteristics of ARIC Study Participants by Attrition Status at Visit 5.

|  |  |  |  |
| --- | --- | --- | --- |
|  | Alive and attended visit 5 | Alive and did not attend visit 5 | Dead prior to visit 5 |
| N | 5,879 | 3,480 | 3,685 |
| 25(OH)D (ng/ml), mean (SD) | 24.6 (8.4) | 24.5 (8.7) | 23.7 (8.7) |
| Cognitive Test Scores, mean (SD) |  |  |  |
| Global Z-Score | 0.3 (0.9) | 0.0 (0.9) | -0.3 (1.0) |
| DWRT Z-Score | 0.2 (0.9) | 0.0 (1.0) | -0.3 (1.0) |
| DWRT Raw Score (words) | 6.9 (1.4) | 6.7 (1.5) | 6.2 (1.6) |
| DSST Z-Score | 0.3 (0.9) | 0.0 (0.9) | -0.4 (1.0) |
| DSST Raw Score (points) | 48.3 (13.4) | 44.8 (13.4) | 39.4 (14.5) |
| WFT Z-Score | 0.2 (1.0) | -0.0 (1.0) | -0.2 (1.0) |
| WFT Raw Score (words) | 35.1 (12.2) | 32.7 (12.1) | 31.0 (12.8) |
| Age (years), mean (SD) | 55.0 (5.1) | 57.3 (5.7) | 59.6 (5.5) |
| 24(OH)D (ng/ml) |  |  |  |
| <20 | 1,405 (23.9) | 864 (24.8) | 778 (21.1) |
| 20-<30 | 2,686 (45.7) | 1,510 (43.4) | 1,568 (42.6) |
| ≥ 30 | 1,788 (30.4) | 1,106 (31.8) | 1,339 (36.3) |
| Female, n (%) | 3,529 (60.0) | 2,159 (62.0) | 1,698 (46.1) |
| Race/Center, n (%) |  |  |  |
| Minneapolis, MN Whites | 1,777 (30.2) | 909 (26.1) | 843 (22.9) |
| Washington County, MD Whites | 1,219 (20.7) | 646 (18.6) | 957 (26.0) |
| Forsyth County, NC Whites | 1,604 (27.3) | 807 (23.2) | 963 (26.1) |
| Forsyth County, NC Blacks | 86 (1.5) | 140 (4.0) | 118 (3.2) |
| Jackson, MS Blacks | 1,193 (20.3) | 978 (28.1) | 804 (21.8) |
| Educationa, n (%) |  |  |  |
| <High School | 842 (14.3) | 813 (23.4) | 1,132 (30.7) |
| High School, GED, or Vocational School | 2,493 (42.4) | 1,509 (43.4) | 1,451 (39.4) |
| College, Graduate, or Professional School | 2,544 (43.3) | 1,158 (33.3) | 1,102 (29.9) |
| BMI (kg/m2), mean (SD) | 27.7 (5.1) | 28.1 (5.4) | 28.3 (5.8) |
| Physical activity indexa, mean (SD) | 2.5 (0.8) | 2.4 (0.8) | 2.4 (0.8) |
| Smoking Status, n (%) |  |  |  |
| Never | 2,684 (45.7) | 1,501 (43.2) | 1,074 (29.2) |
| Former | 2,243 (38.2) | 1,266 (36.4) | 1,397 (38.0) |
| Current | 942 (16.1) | 711 (20.4) | 1,205 (32.8) |
| Alcohol Consumption, n (%) |  |  |  |
| Never | 1,300 (22.2) | 887 (25.5) | 778 (21.2) |
| Former | 992 (16.9) | 718 (20.6) | 998 (27.1) |
| Current | 3,575 (60.9) | 1,872 (53.8) | 1,902 (51.7) |
| Systolic Blood Pressure (mmHg), mean (SD) | 117.8 (16.7) | 121.8 (18.0) | 127.0 (21.4) |
| Diastolic Blood Pressure (mmHg), mean (SD) | 72.0 (9.8) | 71.9 (10.1) | 72.6 (11.3) |
| Use of Hypertension Medications, n (%) | 1,197 (20.4) | 956 (27.5) | 1,352 (37.0) |
| Total Cholesterol (mg/dl), mean (SD) | 207.6 (37.1) | 213.7 (39.5) | 210.7 (42.7) |
| HDL Cholesterol (mg/dl), mean (SD) | 51.2 (16.7) | 50.2 (16.7) | 47.0 (16.7) |
| Use of Cholesterol Medications, n (%) | 304 (5.2) | 232 (6.7) | 294 (8.0) |
| Diabetes, n (%) | 507 (8.6) | 471 (13.6) | 935 (25.4) |
| Cardiovascular Disease, n (%) | 150 (2.6) | 137 (4.0) | 461 (12.8) |
| Estimated Glomerular Filtration Rate <60 mL/min/1.73 m2, n (%) | 98.1 (14.0) | 96.9 (14.6) | 92.8 (18.8) |
| Parathyroid hormone (pg/ml), mean (SD) | 41.8 (16.6) | 42.1 (16.5) | 44.3 (34.6) |
| Calcium (mg/dl), mean (SD) | 9.3 (0.4) | 9.4 (0.4) | 9.4 (0.5) |
| Phosphate (mg/dl), mean (SD) | 3.5 (0.5) | 3.5 (0.5) | 3.5 (0.5) |

aMeasured at ARIC Visit 1 (1987-1989).

Appendix Table 3. Average 20-Year Decline and Difference in 20-Year Decline in Global Cognitive Z Score By 25(OH)D Group Comparing Methods of Accounting for Attrition, ARIC Study (1990-1992 to 2011-2013).

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  | 20-Year Decline | | | Difference 25(OH)D 20-<30 ng/ml versus ≥30 ng/ml | Difference 25(OH)D <20 ng/ml versus ≥30 ng/ml |
|  | N | 25(OH)D ≥30 ng/ml | 25(OH)D 20-<30 ng/ml | 25(OH)D <20 ng/ml |  |  |
| **Overall** |  |  |  |  |  |  |
| Complete data at visit 2 | 12,761 | -0.663 (-0.763, -0.562) | -0.686 (-0.787, -0.585) | -0.699 (-0.806, -0.591) | -0.023 (-0.068, 0.022) | -0.036 (-0.089, 0.017) |
| Complete data at visit 2 and attended visits 2, 4 and 5 | 5,535 | -0.682 (-0.789, -0.575) | -0.705 (-0.813, -0.597) | -0.721 (-0.836, -0.606) | -0.023 (-0.071, 0.024) | -0.039 (-0.095, 0.017) |
| Imputation for covariates only | 12,917 | -0.665 (-0.765, -0.564) | -0.688 (-0.789, -0.587) | -0.695 (-0.803, -0.588) | -0.024 (-0.068, 0.021) | -0.031 (-0.084, 0.022) |
| Imputation for covariates and outcome among those alive at time of visit 5 | 9, 359 | -0.727 (-0.838, -0.616) | -0.765 (-0.875, -0.656) | -0.750 (-0.864, -0.636) | -0.038 (-0.086, 0.009) | -0.023 (-0.080, 0.034) |
|  |  |  |  |  |  |  |
| **Whites** |  |  |  |  |  |  |
| Complete data at visit 2 | 9,764 | -0.607 (-0.721, -0.492) | -0.626 (-0.743, -0.509) | -0.607 (-0.733, -0.481) | -0.019 (-0.065, 0.027) | -0.001 (-0.057, 0.056) |
| Complete data at visit 2 and attended visits 2, 4 and 5 | 4,380 | -0.613 (-0.734, -0.493) | -0.633 (-0.756, -0.510) | -0.617 (-0.750, -0.484) | -0.020 (-0.068, 0.028) | -0.004 (-0.064, 0.056) |
| Imputation for covariates only | 9,849 | -0.610 (-0.724, -0.496) | -0.629 (-0.746, -0.512) | -0.606 (-0.732, -0.480) | -0.019 (-0.065, 0.027) | 0.004 (-0.053, 0.061) |
| Imputation for covariates and outcome among those alive at time of visit 5 | 7,268 | -0.655 (-0.780, -0.529) | -0.684 (-0.811, -0.558) | -0.654 (-0.788, -0.520) | -0.029 (-0.079, 0.020) | 0.001 (-0.060, 0.061) |
|  |  |  |  |  |  |  |
| **Blacks** |  |  |  |  |  |  |
| Complete data at visit 2 | 2,997 | -0.654 (-0.945, -0.363) | -0.777 (-1.017, -0.536) | -0.868 (-1.109, -0.627) | -0.123 (-0.317, 0.072) | **-0.214 (-0.406, -0.023)** |
| Complete data at visit 2 and attended visits 2, 4 and 5 | 1,155 | -0.668 (-0.992, -0.343) | -0.796 (-1.064, -0.529) | -0.898 (-1.167, -0.629) | -0.129 (-0.342, 0.085) | **-0.230 (-0.441, -0.019)** |
| Imputation for covariates only | 3,068 | -0.654 (-0.945, -0.363) | -0.784 (-1.024, -0.543) | -0.868 (-1.109, -0.626) | -0.130 (-0.325, 0.064) | **-0.214 (-0.405, -0.022)** |
| Imputation for covariates and outcome among those alive at time of visit 5 | 2,091 | -0.746 (-1.073, -0.420) | -0.880 (-1.162, -0.597) | -0.893 (-1.174, -0.612) | -0.134 (-0.321, 0.054) | -0.147 (-0.333, 0.039) |

Model adjusted for demographic variables: age, age2, sex, race/center, education, body mass index, smoking status, physical activity, and apolipoprotein ϵ4 genotype, and interactions between each of these variables and time.

Appendix Table 4. Average Adjusteda 6-Year Decline and Difference in 6-Year Decline in Global Cognitive Z-Score By 25(OH)D Group, ARIC Study (1990-1992 to 1996-1998).

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | 6-Year Decline | | | Difference 25(OH)D 20-<30 ng/ml versus ≥30 ng/ml | Difference 25(OH)D <20 ng/ml versus ≥30 ng/ml |
|  | 25(OH)D ≥30 ng/ml | 25(OH)D 20-<30 ng/ml | 25(OH)D <20 ng/ml |  |  |
| **Overall**  (N=13,044) |  |  |  |  |  |
| Model 1 | -0.104 (-0.174, -0.035) | -0.091 (-0.164, -0.018) | -0.106 (-0.183, -0.030) | 0.014 (-0.018, 0.045) | -0.002 (-0.037, 0.034) |
| Model 2 | -0.126 (-0.201, -0.050) | -0.109 (-0.187, -0.031) | -0.122 (-0.204, -0.041) | 0.017 (-0.015, 0.049) | 0.004 (-0.032, 0.039) |
| Model 3 | -0.126 (-0.205, -0.048) | -0.110 (-0.191, -0.029) | -0.124 (-0.207, -0.041) | 0.016 (-0.016, 0.048) | 0.002 (-0.034, 0.038) |
|  |  |  |  |  |  |
| **Whites**  (n=9,878) |  |  |  |  |  |
| Model 1 | -0.073 (-0.149, 0.003) | -0.063 (-0.143, 0.017) | -0.075 (-0.161, 0.011) | 0.011 (-0.020, 0.042) | -0.002 (-0.041, 0.037) |
| Model 2 | -0.096 (-0.178, -0.014) | -0.083 (-0.167, 0.001) | -0.093 (-0.183, -0.003) | 0.013 (-0.018, 0.044) | 0.003 (-0.036, 0.042) |
| Model 3 | -0.097 (-0.181, -0.013) | -0.085 (-0.171, 0.001) | -0.096 (-0.188, -0.004) | 0.012 (-0.019, 0.043) | 0.001 (-0.038, 0.004) |
|  |  |  |  |  |  |
| **Blacks**  (n=3,166) |  |  |  |  |  |
| Model 1 | -0.144 (-0.328, 0.040) | -0.108 (-0.271, 0.055) | -0.125 (-0.288, 0.038) | 0.035 (-0.094, 0.164) | 0.019 (-0.106, 0.144) |
| Model 2 | -0.167 (-0.359, 0.025) | -0.128 (-0.299, 0.043) | -0.144 (-0.315, 0.027) | 0.040 (-0.089, 0.169) | 0.023 (-0.104, 0.150) |
| Model 3 | -0.161 (-0.355, 0.033) | -0.122 (-0.296, 0.052) | -0.140 (-0.312, 0.032) | 0.038 (-0.091, 0.167) | 0.021 (-0.106, 0.148) |

aModel 1: Demographic, behavioral/socioeconomic, and genetic variables including: age, age2, sex, race/center, education, body mass index, smoking status, physical activity, and apolipoprotein ϵ4 genotype, and interactions between each of these variables and time.

Model 2: Model 1 + Cardiovascular factors including: systolic blood pressure, use of hypertension medication, total cholesterol, HDL cholesterol, use of cholesterol medications, diabetes, cardiovascular disease, estimated glomerular filtration rate, and interactions between each of these variables and time.

Model 3: Model 2 + Biomarker mediators in the metabolic pathway including: parathyroid hormone, calcium, phosphorus, and interactions between each of these variables and time.

Appendix Table 5. Average Adjusteda 14-Year Decline and Difference in 14-Year Decline in Global Cognitive Z-Score By 25(OH)D Group, ARIC Study (1996-1998 to 2011-2013).

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | 14-Year Decline | | | Difference 25(OH)D 20-<30 ng/ml versus ≥30 ng/ml | Difference 25(OH)D <20 ng/ml versus ≥30 ng/ml |
|  | 25(OH)D ≥30 ng/ml | 25(OH)D 20-<30 ng/ml | 25(OH)D <20 ng/ml |  |  |
| **Overall**  (N=13,044) |  |  |  |  |  |
| Model 1 | -0.644 (-0.777, -0.510) | -0.686 (-0.815, -0.557) | -0.677 (-0.814, -0.540) | -0.042 (-0.094, 0.010) | -0.033 (-0.101, 0.034) |
| Model 2 | -0.690 (-0.835, -0.546) | -0.729 (-0.870, -0.588) | -0.721 (-0.870, -0.571) | -0.039 (-0.090, 0.013) | -0.030 (-0.098, 0.037) |
| Model 3 | -0.682 (-0.828, -0.535) | -0.720 (-0.861, -0.578) | -0.715 (-0.864, -0.565) | -0.038 (-0.091, 0.014) | -0.033 (-0.102, 0.035) |
|  |  |  |  |  |  |
| **Whites**  (n=9,878) |  |  |  |  |  |
| Model 1 | -0.648 (-0.797, -0.499) | -0.683 (-0.828, -0.538) | -0.657 (-0.814, -0.500) | -0.035 (-0.088, 0.018) | -0.009 (-0.082, 0.064) |
| Model 2 | -0.704 (-0.869, -0.539) | -0.737 (-0.898, -0.576) | -0.711 (-0.883, -0.539) | -0.032 (-0.085, 0.021) | -0.007 (-0.080, 0.066) |
| Model 3 | -0.711 (-0.876, -0.546) | -0.741 (-0.902, -0.580) | -0.716 (-0.887, -0.545) | -0.030 (-0.085, 0.025) | -0.005 (-0.079, 0.069) |
|  |  |  |  |  |  |
| **Blacks**  (n=3,166) |  |  |  |  |  |
| Model 1 | -0.585 (-0.928, -0.242) | -0.722 (-1.008, -0.436) | -0.739 (-1.015, -0.463) | -0.137 (-0.343, 0.069) | -0.154 (-0.360, 0.052) |
| Model 2 | -0.613 (-0.964, -0.262) | -0.749 (-1.043, -0.455) | -0.764 (-1.050, -0.478) | -0.136 (-0.340, 0.068) | -0.151 (-0.355, 0.053) |
| Model 3 | -0.575 (-0.928, -0.222) | -0.711 (-1.009, -0.413) | -0.737 (-1.025, -0.449) | -0.135 (-0.341, 0.071) | -0.162 (-0.368, 0.044) |

aModel 1: Demographic, behavioral/socioeconomic, and genetic variables including: age, age2, sex, race/center, education, body mass index, smoking status, physical activity, and apolipoprotein ϵ4 genotype, and interactions between each of these variables and time.

Model 2: Model 1 + Cardiovascular factors including: systolic blood pressure, use of hypertension medication, total cholesterol, HDL cholesterol, use of cholesterol medications, diabetes, cardiovascular disease, estimated glomerular filtration rate, and interactions between each of these variables and time.

Model 3: Model 2 + Biomarker mediators in the metabolic pathway including: parathyroid hormone, calcium, phosphorus, and interactions between each of these variables and time.

Appendix Table 6. Average Adjusted 20-Year Decline and Difference in 20-Year Decline in Global Cognitive Z-Score By 25(OH)D Group Using Cut-Points of 10 ng/ml and 20 ng/ml, ARIC Study (1990-1992 to 2011-2013).

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | 20-Year Decline | | | Difference 25(OH)D 10-<20 ng/ml versus ≥20 ng/ml | Difference 25(OH)D <10 ng/ml versus ≥20 ng/ml |
|  | 25(OH)D ≥20 ng/ml | 25(OH)D 10-<20 ng/ml | 25(OH)D<10 ng/ml |  |  |
| Overall  (N=13,044) | -0.743 (-0.857, -0.629) | -0.738 (-0.860, -0.617) | -0.788 (-0.954, -0.622) | 0.005 (-0.041, 0.051) | -0.045 (-0.170, 0.080) |
| Whites  (n=9,878) | -0.662 (-0.791, -0.534) | -0.635 (-0.776, -0.494) | -0.817 (-1.057, -0.576) | 0.027 (-0.025, 0.080) | -0.154 (-0.356, 0.047) |
| Blacks  (n=3,166) | -0.838 (-1.135, -0.541) | -0.879 (-1.177, -0.581) | -0.850 (-1.185, -0.515) | -0.041 (-0.138, 0.056) | -0.012 (-0.191, 0.167) |

Model adjusted for demographic variables: age, age2, sex, race/center, education, body mass index, smoking status, physical activity, and apolipoprotein ϵ4 genotype, and interactions between each of these variables and time.

Appendix Table 7. Average Adjusted 20-Year Decline and Difference in 20-Year Decline in Global Cognitive Z-Score By 25(OH)D Group Excluding Those with Global Cognitive Z-Score Less Than -2 SD at Baseline, ARIC Study (1990-1992 to 2011-2013).

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | 20-Year Decline | | | Difference 25(OH)D 20-<30 ng/ml versus ≥30 ng/ml | Difference 25(OH)D <20 ng/ml versus ≥30 ng/ml |
|  | 25(OH)D ≥30 ng/ml | 25(OH)D 20-<30 ng/ml | 25(OH)D < 20 ng/ml |  |  |
| **Overall**  (N=11,035) | -0.726 (-0.840, -0.612) | -0.764 (-0.879, -0.650) | -0.749 (-0.869, -0.629) | -0.038 (-0.088, 0.011) | -0.023 (-0.080, 0.035) |
| **Whites**  (n=9,067) | -0.661 (-0.791, -0.531) | -0.691 (-0.824, -0.558) | -0.659 (-0.801, -0.517) | -0.030 (-0.081, 0.021) | 0.002 (-0.060, 0.065) |
| **Blacks**  (n=1,968) | -0.726 (-1.073, -0.379) | -0.867 (-1.161, -0.573) | -0.897 (-1.190, -0.605) | -0.141 (-0.352, 0.070) | -0.171 (-0.376, 0.033) |

Model adjusted for demographic variables: age, age2, sex, race/center, education, body mass index, smoking status, physical activity, and apolipoprotein ϵ4 genotype, and interactions between each of these variables and time.