Vitamin E in aging persons with Down syndrome

A randomized, placebo-controlled clinical trial

Mary Sano, PhD
Paul S. Aisen, MD
Howard F. Andrews, PhD
Wei-Yann Tsai, PhD
Florence Lai, MD
Arthur J. Dalton, PhD
For the International
Down Syndrome and
Alzheimer's Disease
Consortium

Correspondence to
Dr. Sano:
mary.sano@mssm.edu

ABSTRACT

Objective: To determine whether vitamin E would slow the progression of cognitive deterioration and dementia in aging persons with Down syndrome (DS).

Methods: A randomized, double-blind controlled clinical trial was conducted at 21 clinical sites, and researchers trained in research procedures recruited adults with DS older than 50 years to participate. Participants were randomly assigned to receive 1,000 IU of vitamin E orally twice daily for 3 years or identical placebo. The primary outcome was change on the Brief Praxis Test (BPT). Secondary outcomes included incident dementia and measures of clinical global change, cognition, function, and behavior.

Results: A total of 337 individuals were randomized, 168 to vitamin E and 169 to placebo. Both groups demonstrated deterioration on the BPT with no difference between drug and placebo. At baseline, 26% were diagnosed with dementia and there was an overall rate of incident dementia of 11%/year with no difference between groups. There was no effect on the secondary outcome measures. Though numerically higher in the treatment group, there was no difference in the number of adverse events ($p = 0.079$) and deaths ($p = 0.086$) between groups.

Conclusions: Vitamin E did not slow the progression of cognitive deterioration in older individuals with DS.

Classification of evidence: This study provides Class II evidence that vitamin E does not significantly slow the progression of cognitive deterioration in aging persons with DS. *Neurology*® 2016;86:2071-2076

GLOSSARY

AD = Alzheimer disease; **AE** = adverse events; **BPT** = Brief Praxis Test; **CGI-C** = Clinical Global Impression of Change; **DS** = Down syndrome; **DSM-IV** = *Diagnostic and Statistical Manual of Mental Disorders, 4th edition*; **GEE** = generalized estimating equations; **ICD-9** = *International Classification of Diseases-9*; **ID** = intellectual disability; **IRB** = institutional review board; **SAE** = serious adverse events.

Individuals with Down syndrome (DS) are uniquely vulnerable to Alzheimer disease (AD), with reports that those 35–40 years of age show key neuropathologic changes characteristic of AD^{1–3} and clinical signs of dementia around the age of 50 years.^{4,5} With increasing life expectancy,⁶ there is a growing need to identify appropriate interventions. While there are approved treatments for AD, which have been assessed in those with DS,^{7,8} there is little established methodology for preventing or treating cognitive loss in DS or in reducing incipient dementia.

Oxidative stress as a mechanism of pathology in both AD and the DS brain is supported by studies demonstrating oxidative damage in Alzheimer brain^{9–11} and by in vitro studies identifying the role of free radicals in neuronal damage in DS^{12,13} and peripheral markers of oxidative stress in DS.^{14,15} Given these reports, it is reasonable to explore antioxidant treatment strategies in aging individuals with DS.

Supplemental data
at *Neurology.org*

From the Department of Psychiatry (M.S.), Alzheimer Disease Research Center, Icahn School of Medicine at Mount Sinai, New York; James J. Peters VAMC (M.S.), Bronx, NY; Alzheimer's Therapeutic Research Institute (P.S.A.), University of Southern California, San Diego; Data Coordinating Center (H.F.A.), New York State Psychiatric Institute; Department of Psychiatry (H.F.A.) and Division of Biostatistics (W.-Y.T.), Columbia University College of Physicians and Surgeons, New York, NY; Department of Neurology (F.L.), McLean Hospital, Belmont; Harvard Medical School (F.L.), Boston, MA; and Center for Aging Studies (A.J.D.), George Jervis Clinic, New York State Institute for Basic Research in Developmental Disabilities, Staten Island.

Coinvestigators are listed on the *Neurology*® Web site at *Neurology.org*.

Go to *Neurology.org* for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Evidence that the antioxidant vitamin E may have a therapeutic role in cognitive disorders is mixed. Two clinical trials of individuals with AD demonstrated slower clinical progression and less functional deterioration over multiple years.^{16,17} However, another trial in those with mild cognitive impairment demonstrated no benefit of vitamin E in slowing cognitive loss or reducing the transition to AD.¹⁸ Based on these data, the primary hypothesis was that high-dose vitamin E would slow clinical deterioration in aging persons with DS over a 3-year period, presumably through its antioxidant action.

A major challenge to assessing vitamin E in DS is selection of the appropriate population and outcome. The trials with evidence of a benefit of vitamin E focused on noncognitive outcomes. In addition, individuals with DS have limited capacity to be assessed with traditional cognitive measures and therefore this study chose to use the Brief Praxis Test, a measure sensitive to longitudinal change in an aging DS population and useful in individuals with a wide range of intellectual developmental delay.^{19,20}

METHODS Participants. The trial recruited participants with DS, for whom English was their primary language, aged 50 years or older, with or without dementia as determined by medical examination who were medically stable with stable medication for 3 months or more. Participants were community-dwelling, living at home or in residential (but not skilled nursing) facilities. Exclusion criteria included inability to score a minimum of 20 points on the Brief Praxis Test (BPT), major depression within the past 3 months, evidence of vascular dementia, a history of coagulopathy, use of anticoagulants, and vitamin E use (at a dose greater than 50 IU/day) in the previous 6 months. The use of stable doses of approved treatments for dementia was permitted. A stable study partner with adequate knowledge of the participant's day-to-day function was identified for each participant. This could have been a family member or a paid care provider. Study conduct was done through a collaboration of international clinical research sites with research experience in adult individuals with DS.²¹ Recruitment occurred at 21 sites in 5 countries.

Standard protocol approvals, registrations, and patient consents. The overall study was approved by the institutional review board (IRB) of the Research Foundation for Mental Hygiene. An IRB or regional ethics review board approved the study at each site and prior to any procedures; informed consent was obtained in accordance with local standards and requirements. In general, individuals with DS of this age group had a clearly identified legally authorized representative who provided consent and all participants provided assent. The trial was registered at clinicaltrials.gov (NCT00056329).

Primary outcome measure. The primary outcome measure, the BPT, has demonstrated sensitivity to change over time in aging persons with DS.^{19,20} It has been validated as a measure of clinical status and cognitive function in both cross-sectional and longitudinal studies.²² Standardized training on the outcome measures was completed by each blinded assessor at all clinical sites via both in-person and video training. Site staff were certified to conduct the outcome after demonstrating administration and scoring competence on a test video.

Secondary outcome measures. Secondary outcome measures (described in detail elsewhere¹⁹) included memory tests, both verbal and visual (modified Fuld Object Memory Test, New Dot Test), Vocabulary Test, Orientation Test, The Behavior & Function Questionnaire, and the Clinical Global Impression of Change (CGI-C). Dementia was assessed at each visit in those who did not have a diagnosis of dementia, using criteria from the DSM-IV.

Safety assessment. Vital signs, medical examination, a symptom checklist, and adverse event reporting were captured to assess safety at each visit.

Intervention. Randomization to vitamin E 1,000 IU orally twice daily or placebo occurred in a 1:1 ratio for 3 years. Participants were also provided with a one-a-day multivitamin. Medication adherence was supervised by the study partner. Medication was returned and counted on site. In cases of less than 80% compliance, study partners were instructed to insure medication adherence.

Randomization and blind. In this parallel-group trial, randomization to vitamin E or placebo, in a 1:1 ratio, was conducted centrally. Assignment was stratified by site and by presence of AD. This was a double-blind study. Participants, study partners, and site personnel did not know whether the participant was receiving active medication or placebo. Staff at the sites and at the Data Coordinating Center were blind to treatment assignment with the exception of staff members who prepared the randomization scheme.

Procedures. Participants were characterized by medical and neurologic evaluation including laboratory studies for hematology, chemistry, folate, B₁₂, syphilis serology (rapid plasma reagin), thyroid function assessment (thyroid-stimulating hormone or free thyroxine index), and prothrombin time to ensure medical stability and to rule out other causes of dementia. *APOE* genotype analysis was also done due to its effect on AD risk ($\epsilon 4$ allele increases risk and $\epsilon 2$ allele decreases risk).^{23,24} Level of lifelong intellectual disability (ID) (mild, moderate, severe, or profound) and trisomy 21 status was collected from record review. A structured evaluation was completed by a study physician to determine dementia diagnosis using DSM-IV criteria for Alzheimer Disease²⁵ and ICD-9²⁶ criteria for dementia. Participants were randomized at baseline and after randomization all outcomes were collected at 6-month intervals. All data were monitored on site by centralized monitors who reported to the Data Coordinating Center.

Data analysis. The primary research question was as follows: Does vitamin E slow the clinical deterioration of aging in persons with DS, assessed with an intent-to-treat analysis, which included all participants according to initial group assignment at randomization? Group differences at baseline in clinical and demographic variables were examined with *t* test or χ^2 . Planned analysis called for examination of imbalance between groups for sex, age, ID status, presence of dementia, and *APOE* $\epsilon 4$ allele.

Figure 1 Consolidated Standards of Reporting Trials flow diagram

These variables would be included in the primary analysis, which used the generalized estimating equations (GEE) to assess BPT scores and other outcomes. GEE permits the use of all available data. Chi-square was used for the secondary analysis of incident dementia.

Sample size estimate was set at approximately 200 in each group, based on an effect size of one third reduction in mean 3-year change score, with a desired power of between 95% and 97% using the GEE method and anticipating a 10% dropout rate. The same sample size provided between 79% and 83% power for the observation of a 0.25 effect size.

RESULTS The first participant in this study was randomized on May 21, 2002. The last participant was completed on April 12, 2010, with the end of the trial. A total of 349 participants were screened and 337 were randomized and available for the analysis of the primary outcome. The Consolidated Standards of Reporting Trials flow diagram (figure 1) is provided. The majority of those randomized (table 1) were male (202/337; 60%), were white non-Hispanic (328/337; 97%), had mild to moderate level of ID (224/304; 74%), did not have dementia (249/337; 74%), and were living in a residential facility (249/337; 74%). Dementia medication use was rare (memantine 3/337 and donepezil 6/337). There were no differences between vitamin E and placebo groups on these demographic features,

though there was a higher percentage of female participants in the treated group than in the placebo group, which approached significance (45% vs 35%; $p = 0.06$), and this variable was included in the model.

Results of primary outcome. BPT are provided in figure 2. The vitamin E and placebo groups did not differ in the rate of change (GEE: $b = 0.159$; confidence interval -0.732 to 1.049 ; $p = 0.729$).

Results of secondary outcomes. No differences were observed between drug and placebo on any of the

Table 1 Characteristics at baseline by treatment group assignment

	Vitamin E (n = 168)	Placebo (n = 169)	p Value
Male	55	65	0.06
Mean age, y (SD)	54.82 (4.75)	54.09 (3.74)	0.31
One or more APOE ϵ 4 alleles, %	15	23	0.79
Dementia diagnosis, %	28	24	0.26
Severe or profound mental retardation, %	46	34	0.16

Figure 2 Results of primary outcome: Brief Praxis Test (BPT)

Data are reported as raw score at each assessment interval. The active group received 2,000 IU vitamin E daily. The placebo group received a comparable capsule.

secondary outcome measures, as shown in table 2. On the CGI-C, the majority of participants showed no change or worsening, with no difference between the groups (figure 3: CGI-C). The vitamin E group had 44 cases of incident dementia (37%) and the placebo group had 36 (29%); this difference was not significant ($p = 0.22$).

Results of safety assessments. Nonserious adverse events (AE) were common; 96% of the treatment group vs 93% of the placebo group had one or more AE, but the difference was not significant ($p = 0.90$). Most common were diarrhea, depression/crying, and joint pain (table e-1 on the *Neurology*[®] Web site at Neurology.org). There was also no difference between groups in the number of patients who experienced serious AE (SAE) such as medical conditions that required hospitalization or significant treatment or care (drug 31.5% vs placebo 32%; $p = 1.00$). However, there were more deaths in the treatment (28) than placebo (16) group (17% vs 10%) and this difference approached significance ($p = 0.086$). None were deemed related to treatment. The most commonly

reported cause of death was pneumonia/respiratory failure (8 in placebo, 14 in treatment), cardiac arrest (4 in placebo, 5 in treatment), and cerebral hemorrhage (3 in treatment group).

Additional analyses examined subgroups of those with and without dementia at baseline with no indication of vitamin E/placebo difference on the BPT or secondary outcomes (data not shown).

DISCUSSION Vitamin E did not slow the progression of cognitive deterioration in DS. The lack of efficacy was observed across cognitive, functional, behavioral, and clinical global outcomes. It was observed in all planned subgroups, including those with and without dementia, and those with and without an *APOE* $\epsilon 4$ allele. This study was based on animal and cell culture studies that indicate that lowering oxidative stress will reduce neurodegeneration.^{27–29} While the study was also based on a trial demonstrating slowing of clinical decline in moderately impaired individuals with AD, the present results parallel those of recent reports of no improvement in cognition with antioxidant combinations that included lower dose of vitamin E in other populations³⁰ as well as in adults with DS.³¹ We did not measure antioxidant activity in this study, though a recent report describes lowering of CSF isoprostane, a marker of antioxidant function, with vitamin E in combination with other vitamins. That report described borderline worsening of clinical outcomes.¹⁷

While the number of AE and SAE were higher in the treatment group, the difference was not significant. Of particular note is that this and other reports³² have identified trends toward worsening outcomes, including death and cardiovascular events. This is in contrast to recent findings in those with AD who show no difference or a trend toward better survival.¹⁷ This profile must be considered when planning future trials with this agent.

Results in this study of adults with DS over 50 years of age indicate that fewer than a third had dementia at baseline and another third had incident

Table 2 Results of secondary outcome measures

Test	Treatment		Placebo		p Value
	Baseline	Final	Baseline	Final	
Fuld recognition	7.7 ± 2.6 (n = 162)	7.7 ± 2.9 (n = 99)	8.0 ± 2.3 (n = 164)	7.6 ± 3.2 (n = 114)	0.392
Fuld recall	20.2 ± 16.1 (n = 153)	25.2 ± 18.3 (n = 96)	21.5 ± 16.1 (n = 155)	25.4 ± 18.5 (n = 109)	0.744
New dot test	1.5 ± 1.6 (n = 151)	1.5 ± 2.0 (n = 97)	1.5 ± 1.7 (n = 159)	1.2 ± 1.7 (n = 108)	0.094
Vocabulary	28.2 ± 17.2 (n = 162)	26.7 ± 19.6 (n = 104)	31.7 ± 18.5 (n = 165)	29.9 ± 20.5 (n = 113)	0.918
Behavior and function	78.9 ± 18.5 (n = 168)	69.5 ± 22.8 (n = 112)	81.4 ± 17.8 (n = 169)	71.0 ± 23.4 (n = 126)	0.921
Orientation	2.1 ± 2.6 (n = 158)	1.7 ± 2.4 (n = 104)	2.7 ± 2.9 (n = 164)	1.9 ± 2.3 (n = 116)	0.478

Figure 3 Clinical Global Impression of Change

Data are reported as percent of group reporting each level of change. The active group received 2,000 IU vitamin E daily. The placebo group received a comparable capsule.

dementia over the full study period. This agrees with the rates reported in studies of similar-aged adults with DS.^{4,33–35} This is in contrast with the 15% reported in a longitudinal study.³⁶ However, only high-functioning (mean IQ 52) participants without dementia were included in that study.

We found a rapid rate of conversion to dementia of about 11% per year, supporting the accepted fact that dementia is a serious risk among aging individuals with DS. Nevertheless, the rate of clinical dementia never matched the reported universality of the neuropathologic hallmarks of AD in the brains of those with DS.

This international multisite clinical trial consortium in DS demonstrated effective ability to recruit and retain this challenging population in a multiyear study. Comprehensive assessment of clinical and cognitive outcomes was also accomplished and the selected outcomes demonstrated sensitivity to change over time. Regardless of dementia status or severity of disability, the outcome measures captured deterioration in aging individuals with DS. The CGI-C, adapted for adults with DS, demonstrated sensitivity to worsening, though it was not affected by vitamin E.

The consortium was able to establish the mechanism to identify individuals and to collect appropriate informed consent. A major concern with this population is the high likelihood of limited decisional capacity for clinical trial participation. However, the

research experience of the clinical sites provided an advantage in that they were able to engage families and legally authorized representatives to evaluate the research risks and benefits, to weigh the decisions for participation, and to provide consent when appropriate. The sites created partnerships with participants, families, and public and private agencies that resulted in committed participation in this clinical trial and potential enthusiasm for consideration of future research to address important clinical needs. With many similarities between AD in DS and AD in the general population, studies in one population may inform the other. This is especially important in view of the delay in clinical expression of the dementia despite the neuropathology of AD, and a window of opportunity to intervene. With the infrastructure in place, it will be easier to include adults with DS in future clinical trials of AD treatments.

While the population is comparable to many with DS of this age who live in community-based residential settings, several limitations are worthy of note. We did not confirm trisomy but rather depended on medical record review. Our cohort was of advanced age for a DS population, limiting our knowledge of the usefulness of vitamin E in a young population. We collected no biomarkers of disease pathology, oxidative stress, or vitamin E levels. This was an intentional decision to reduce participant burden and maximize sample size for clinical outcomes. However, it may limit our knowledge of biological pathways associated with clinical decline and with therapeutic efficacy. Future studies might include such biomarkers, particularly as less invasive methods of data collection are developed.

Overall, vitamin E does not benefit cognition or function in aging individuals with DS. Trends toward negative outcomes indicate the need for caution in using this agent in this population.

AUTHOR CONTRIBUTIONS

Dr. Sano contributed to the conception and design of the study, the interpretation of the data, the initial draft, and revising the manuscript. She is the corresponding author and is responsible for submitting the manuscript and for all communications with the journal and ensures that all authors have approved this version and that all authors signed the disclosure agreement. Dr. Aisen contributed to the conception and design of the study, interpretation of the data, and drafting and revising the manuscript. Dr. Andrews contributed to the analysis and interpretation of the data and revising the manuscript. Dr. Tsai contributed to the analysis or interpretation of the data and revising the manuscript. Dr. Lai contributed to the design of the study and to revising the manuscript. Dr. Dalton contributed to the conception or design of the study and the interpretation of the data.

STUDY FUNDING

Supported by grant R01AG16381, A multicenter trial of vitamin E in aging persons with Down syndrome, PI: Arthur Dalton, PhD.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

REFERENCES

- Malamud N. Neuropathology of organic brain: syndromes associated with aging. In: Gaitz CM, editor. *Aging and the Brain*. 3rd ed. New York: Plenum; 1972:63–87.
- Mann DM, Yates PO, Marcyniuk B. Alzheimer's presenile dementia, senile dementia of Alzheimer type and Down's syndrome in middle age form an age related continuum of pathological changes. *Neuropathol Appl Neurobiol* 1984; 10:185–207.
- Wisniewski KE, Wisniewski HM, Wen GY. Occurrence of neuropathological changes and dementia of Alzheimer's disease in Down's syndrome. *Ann Neurol* 1985;17:278–282.
- Lai F, Williams RS. A prospective study of Alzheimer disease in Down syndrome. *Arch Neurol* 1989;46:849–853.
- Janicki MP, Dalton AJ. Prevalence of dementia and impact on intellectual disability services. *Ment Retard* 2000;38:276–288.
- Janicki MP, Dalton AJ, Henderson CM, Davidson PW. Mortality and morbidity among older adults with intellectual disability: health services considerations. *Disabil Rehabil* 1999;21:284–294.
- Hanney M, Prasher V, Williams N, et al. Memantine for dementia in adults older than 40 years with Down's syndrome (MEADOES): a randomized, double-blind, placebo-controlled trial. *Lancet* 2012;379:528–536.
- Kishnani PS, Sommer BR, Handen BL, et al. The efficacy, safety, and tolerability of donepezil for the treatment of young adults with Down syndrome. *Am J Med Genet A* 2009;149A:1641–1654.
- Good PF, Werner P, Hsu A, Olanow CW, Perl DP. Evidence of neuronal oxidative damage in Alzheimer's disease. *Am J Pathol* 1996;149:21–28.
- Smith MA, Perry G, Richey PL, et al. Oxidative damage in Alzheimer's. *Nature* 1996;382:120–121.
- Markesbery WR, Lovell MA. Four-hydroxynonenal, a product of lipid peroxidation, is increased in the brain in Alzheimer's disease. *Neurobiol Aging* 1998;19:33–36.
- Busciglio J, Yankner BA. Apoptosis and increased generation of reactive oxygen species in Down's syndrome neurons in vitro. *Nature* 1995;378:776–779.
- Busciglio J, Pelsman A, Wong C, et al. Altered metabolism of the amyloid beta precursor protein is associated with mitochondrial dysfunction in Down's syndrome. *Neuron* 2002;33:667–688.
- Brugge K, Nichols S, Saitoh T, Trauner D. Correlations of glutathione peroxidase activity with memory impairment in adults with Down syndrome. *Biol Psychiatry* 1999;46:1682–1689.
- Pratico D, Iuliano L, Amerio G, et al. Down's syndrome is associated with increased 8,12-iso-iPF2alpha-VI levels: evidence for enhanced lipid peroxidation in vivo. *Ann Neurol* 2000;48:795–798.
- Sano M, Ernesto C, Thomas RG, et al. A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. *N Engl J Med* 1997;336:1216–1222.
- Dysken MW, Sano M, Asthana S, et al. Effect of vitamin E and memantine on functional decline in Alzheimer disease: the TEAM-AD VA cooperative randomized trial. *JAMA* 2014;311:33–44.
- Petersen RC, Thomas RG, Grudman M, et al. Vitamin E and donepezil for the treatment of mild cognitive impairment. *N Engl J Med* 2005;352:2379–2389.
- Sano MC, Aisen PS, Dalton AJ, Andrews HF, Tsai WY; the International Down Syndrome Alzheimer's Disease Consortium. Assessment of aging individuals with Down syndrome in clinical trials: results of baseline measures. *J Policy Pract Dev Disabil* 2005;2:126–138.
- Lott IT, Doran E, Nguyen VQ, Tournay A, Movsesyan N, Gillen DL. Down syndrome and dementia: seizures and cognitive decline. *J Alzheimers Dis* 2012;29:177–185.
- Aisen PS, Dalton AJ, Sano MC, Lott IT, Andrews HF, Tsai WY. Design and implementation of a multicenter trial of vitamin E in aging individuals with Down syndrome. *Policy Pract Intellect Disabilities* 2005;2:86–93.
- Dalton A, Fedor B. *Dyspraxia Scale for Adults With Down Syndrome*. Staten Island, NY: NYS Institute for Basic Research in Developmental Disabilities; 1997.
- Schupf N, Kapell D, Lee JH, et al. Onset of dementia is associated with apolipoprotein E ε4 in Down syndrome. *Ann Neurol* 1996;40:799–801.
- Lai F, Kamman E, Rebeck GW, Anderson A, Chen Y, Nixon RA. APOE genotype and gender effects on Alzheimer disease in 100 adults with Down syndrome. *Neurology* 1999;53:331–336.
- American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. Washington, DC: American Psychiatric Association; 1994.
- International Classification of Diseases, Ninth Revision, Clinical Modification. Available at: <http://www.who.int/classifications/icd/en/>. Accessed April 27, 2016.
- Halliwell B, Gutteridge JMC. *Free Radicals in Biology and Medicine*. Oxford, UK: Clarendon Press; 1989.
- Bruce AJ, Malfroy B, Baudry M. β-Amyloid toxicity in organotypic hippocampal cultures: protection by EUK-8, a synthetic catalytic free radical scavenger. *Proc Natl Acad Sci USA* 1996;93:2312–2316.
- Tomiyama T, Shoji A, Kataoka K, et al. Inhibition of amyloid β protein aggregation and neurotoxicity by rifampicin: its possible function as a hydroxyl radical scavenger. *J Biol Chem* 1996;271:6839–6844.
- Galasko DR, Peskind E, Clark CM, et al; for the Alzheimer's Disease Cooperative Study. Antioxidants for Alzheimer disease: a randomized clinical trial with cerebrospinal fluid biomarker measures. *Arch Neurol* 2012; 69:836–841.
- Lott IT, Doran E, Nguyen VQ, Tournay A, Head E, Gillen DL. Down syndrome and dementia: a randomized, controlled trial of antioxidant supplementation. *Am J Med Genet A* 2011;155A:1939–1948.
- Miller ER, Pastor-Barriuso R, Dalal D, Riemersma R, Appel LJ, Guallar E. Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. *Ann Intern Med* 2005;142:37–47.
- Zigman WB, Schupf N, Sersen E, Silverman W. Prevalence of dementia in adults with and without Down syndrome. *Am J Ment Retard* 1996;100:403–412.
- Holland AJ, Hon J, Huppert FA, Stevens F, Watson P. Population-based study of the prevalence and presentation of dementia in adults with Down's syndrome. *Br J Psychiatry* 1998;172:493–498.
- Tyrrell J, Cosgrave M, McCarron M, et al. Dementia in people with Down's syndrome. *Int J Geriatr Psychiatry* 2001;16:1168–1174.
- Devenny DA, Krinsky-McHale SJ, Sersen G, Silverman WP. Sequence of cognitive decline in dementia in adults with Down's syndrome. *J Intellect Disabil Res* 2000;44:654–665.