Folic Acid, Pyridoxine, and Cyanocobalamin Combination Treatment and Age-Related Macular Degeneration in Women

The Women's Antioxidant and Folic Acid Cardiovascular Study

William G. Christen, ScD; Robert J. Glynn, ScD; Emily Y. Chew, MD; Christine M. Albert, MD; JoAnn E. Manson, MD

Background: Observational epidemiologic studies indicate a direct association between homocysteine concentration in the blood and the risk of age-related macular degeneration (AMD), but randomized trial data to examine the effect of therapy to lower homocysteine levels in AMD are lacking. Our objective was to examine the incidence of AMD in a trial of combined folic acid, pyridoxine hydrochloride (vitamin B₆), and cyanocobalamin (vitamin B₁₂) therapy.

Methods: We conducted a randomized, double-blind, placebo-controlled trial including 5442 female health care professionals 40 years or older with preexisting cardiovascular disease or 3 or more cardiovascular disease risk factors. A total of 5205 of these women did not have a diagnosis of AMD at baseline and were included in this analysis. Participants were randomly assigned to receive a combination of folic acid (2.5 mg/d), pyridoxine hydrochloride (50 mg/d), and cyanocobalamin (1 mg/d) or placebo. Our main outcome measures included total AMD, defined as a self-report documented by medical record evidence of an initial diagnosis after randomization, and visually significant AMD, defined as confirmed incident AMD with visual acuity of 20/30 or worse attributable to this condition.

Results: After an average of 7.3 years of treatment and follow-up, there were 55 cases of AMD in the combination treatment group and 82 in the placebo group (relative risk, 0.66; 95% confidence interval, 0.47-0.93 [P = .02]). For visually significant AMD, there were 26 cases in the combination treatment group and 44 in the placebo group (relative risk, 0.59; 95% confidence interval, 0.36-0.95 [P = .03]).

Conclusions: These randomized trial data from a large cohort of women at high risk of cardiovascular disease indicate that daily supplementation with folic acid, pyridoxine, and cyanocobalamin may reduce the risk of AMD.

Trial Registration: clinicaltrials.gov Identifier NCT00000161

Arch Intern Med. 2009;169(4):335-341
function independent of the effect of lowering homocys-
teine levels. However, trials of therapy to lower homocysteine levels among persons with preexisting vas-
cular disease provide little support for a benefit of supple-
mental folic acid and B vitamins in reducing cardiovas-
cular events. Nonetheless, given the recent evidence
supporting a link between homocysteine and AMD and
other data suggesting an etiologic role for atherosclerosis
in this arm of the trial and were willing to forego the use of vita-
in supplements may help to decrease the risk of AMD. At present, no previous data exist from large ran-
domized trials to examine this hypothesis.

In this report, we present the results for AMD from
the Women’s Antioxidant and Folic Acid Cardiovascular
Study (WAFACS), a randomized trial that evaluated
whether combined treatment with folic acid, pyridox-
ine, and cyanocobalamin could prevent cardiovascular
events among women at high risk of CVD.

**STUDY DESIGN**

WAFACS was a randomized, double-blind, placebo-controlled trial that evaluated whether a combination of folic acid, pyridoxine, and cyanocobalamin could reduce cardiovascular events among women with preexisting CVD or with 3 or more coronary risk factors. The WAFACS began in 1998, when the treatment arm consisting of folic acid, pyridoxine, and cyanocobalamin was added to the ongoing Women’s Antioxidant Cardiovascular Study (WACS), a 2 × 2 factorial trial of 8171 women at high risk of CVD who were randomized from June 1995 through October 1996 to receive vitamin E, ascorbic acid (vitamin C), beta carotene, or placebos (Figure 1). From August 1997 through January 1998, all 8171 women participating in the WACS were sent invitations and consent forms for participation in the folic acid/pyridoxine/cyanocobalamin (combination treatment) arm of the trial. Of the total cohort, 5442 women were willing and eligible to participate in this arm of the trial and were willing to forego the use of vitamin B supplements or multivitamins with greater than the recommended daily allowance of folic acid, vitamin B₆, and vitamin B₁₂. In April 1998, these women were randomized in a factorial design to a daily combination of folic acid (2.5 mg/d), pyridoxine hydrochloride (vitamin B₆) (50 mg/d), and cyanocobalamin (vitamin B₁₂) (1 mg/d). Of the 8171 women participating in the WACS were sent invitations and consent forms for participation in the folic acid/pyridoxine/cyanocobalamin (combination treatment) arm of the trial. Of the total cohort, 5442 women were willing and eligible to participate in this arm of the trial and were willing to forego the use of vitamin B supplements or multivitamins with greater than the recommended daily allowance of folic acid, vitamin B₆, and vitamin B₁₂. In April 1998, these women were randomized in a factorial design to a daily combination of folic acid (2.5 mg/d), pyridoxine hydrochloride (50 mg/d), and cyanocobalamin (1 mg/d). Of these women, 5205 did not have a diagnosis of AMD at base-

**METHODS**

**Figure 1.** Enrollment and randomization scheme for the folic acid, pyridoxine, and cyanocobalamin component of the Women’s Antioxidant and Folic Acid Cardiovascular Study. Combination treatment indicates folic acid (2.5 mg/d), pyridoxine hydrochloride (vitamin B₆) (50 mg/d), and cyanocobalamin (vitamin B₁₂) (1 mg/d). Of the 8171 women who were randomized, 5442 were willing and eligible to participate in the arm that tested combination treatment vs placebo.
AMD ended in November 2005. Overall, approximately 84.0% of women reported taking at least two-thirds of their study pills during the course of the study, with no significant difference between the active and placebo groups.

ASCERTAINMENT AND DEFINITION OF END POINTS

Women who reported a diagnosis of AMD on the baseline questionnaire were excluded. Information on new diagnoses of AMD was requested on annual questionnaires. Participants were asked, “Since your last questionnaire, have you had any of the following?” with response options including “macular degeneration right eye” and “macular degeneration left eye.” If yes, participants were requested to provide the month and year of the diagnosis and to complete a consent form granting permission to examine medical records pertaining to the diagnosis. Ophthalmologists and optometrists were contacted by mail and requested to complete an AMD questionnaire that asked about the date of the initial diagnosis, the best-corrected visual acuity at the time of diagnosis, and the date when best-corrected visual acuity reached 20/30 or worse (if different from the date of initial diagnosis). Information was also requested about the signs of AMD observed (ie, drusen, retinal pigment epithelium [RPE] hypopigmentation or hyperpigmentation, geographic atrophy, RPE detachment, subretinal neovascular membrane, or disciform scar) when visual acuity was first noted to be 20/30 or worse, and the date when exudative neovascular disease, if present, was first noted (defined by the presence of RPE detachment, subretinal neovascular membrane, or disciform scar). Ophthalmologists and optometrists were also asked whether there were other ocular abnormalities that could explain or contribute to the vision loss and, if so, whether the AMD by itself was significant enough to cause the best-corrected visual acuity to be reduced to 20/30 or worse. As an alternative, they could provide the requested information by supplying photocopies of the relevant medical records. Medical records were obtained for 94.0% of participants reporting AMD.

The following 2 end points were defined: (1) total AMD, defined as a self-report confirmed by medical record evidence of an initial diagnosis after randomization but before July 31, 2005, and (2) visually significant AMD, with the same definition as total AMD but with best-corrected visual acuity loss to 20/30 or worse attributable to AMD.

DATA ANALYSIS

Cox proportional hazards regression was used to estimate the relative risk (RR) of AMD among those assigned to receive the combination treatment compared with those assigned to receive placebo after adjustment for age (in years) at baseline and randomized assignments to ascorbic acid, vitamin E, and beta carotene treatment.19 Models were also fit separately within the prespecified age groups of 40 to 54 years, 55 to 64 years, and 65 years or older. The proportionality assumption throughout the follow-up period was tested by including an interaction term as total AMD but with best-corrected visual acuity loss to 20/30 or worse attributable to AMD.

The baseline characteristics of participants in the combination treatment and placebo groups are shown in Table 1. As expected, characteristics were equally distributed between the 2 treatment groups. During an average of 7.3 years of treatment and follow-up, a total of 137 cases of AMD were documented, including 70 cases of visually significant AMD. Most of the visually significant cases were characterized by some combination of drusen and RPE changes at the time vision was first noted to be 20/30 or worse, reflecting an early
stage of AMD development, as shown in the following tabulation:

<table>
<thead>
<tr>
<th>Signs of AMD</th>
<th>No. (%) of Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drusen only</td>
<td>13 (19)</td>
</tr>
<tr>
<td>RPE changes only</td>
<td>18 (26)</td>
</tr>
<tr>
<td>Drusen and RPE changes</td>
<td>19 (27)</td>
</tr>
<tr>
<td>Geographic atrophy</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Exudative changes(^a)</td>
<td>17 (24)</td>
</tr>
<tr>
<td>Information missing</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Total</td>
<td>70 (100)</td>
</tr>
</tbody>
</table>

\(^a\)Includes RPE detachment, subretinal neovascular membrane, and disciform scar.

For the end point of total AMD, there were 55 cases in the combination treatment group and 82 in the placebo group (RR [adjusted for age and ascorbic acid (vitamin C), vitamin E, and beta carotene treatment assignment], 0.66; 95% CI, 0.47-0.93 [\(P=0.02\)]). For visually significant AMD, there were 26 cases in the combination treatment group and 44 in the placebo group (RR, 0.59; 95% CI, 0.36-0.95 [\(P=0.03\)]). Relative risks did not vary significantly over the 3 age groups for either end point (\(P\) interaction, each > .2).

Cumulative incidence rates of total AMD and visually significant AMD according to the year of follow-up are shown in Figure 2. A beneficial effect of the combination treatment on total AMD began to emerge at approximately 2 years of follow-up and persisted throughout the trial. For visually significant AMD, the curves appeared to diverge later in the trial, at approximately 4 years (Figure 2B). For both end points, the rate differences appeared to increase with longer follow-up. During the first 3 years of follow-up, the RR were 0.87 (95% CI, 0.54-1.42 [\(P=0.59\)]) for total AMD and 0.84 (95% CI, 0.39-1.78 [\(P=0.65\)]) for visually significant AMD. During the remaining 4.3 years of follow-up, the RR were 0.72 (95% CI, 0.44-1.18 [\(P=0.19\)]) for total AMD and 0.52 (95% CI, 0.27-0.98 [\(P=0.04\)]) for visually significant AMD. Tests of proportionality throughout the follow-up period, however, indicated that the proportionality assumption for treatment was not violated for either end point (total AMD, \(P=0.47\); visually significant AMD, \(P=0.42\)).

There was no evidence that the effect of combination treatment on either AMD end point was modified by any AMD risk factor considered. The results for visually significant AMD are shown in Table 2.

**COMMENT**

To our knowledge, this is the first randomized trial to investigate supplemental use of folic acid and B vitamins in the prevention of AMD. The results, based on an average of 7.3 years of treatment and follow-up of women at increased risk of CVD, indicate that those assigned to active treatment had a statistically significant 35% to 40% decreased risk of AMD. The beneficial effect of treatment began to emerge at approximately 2 years of follow-up and persisted throughout the trial.

Support for the hypothesis that therapy consisting of folic acid and B vitamin supplements could lower the risk of AMD has derived largely from observational evidence of a direct association between the homocysteine level in the blood and risk of AMD\(^{16-23}\) and from the demonstration in intervention studies that treatment with folic acid and B vitamin supplements could lower homocysteine levels.\(^{32}\) Further support has been provided by laboratory evidence that the damaging sequelae of elevated homocysteine levels (eg, endothelial dysfunction,\(^{27,29,46}\) impaired vascular reactivity,\(^{28,47,48}\) and promotion of inflammatory processes leading to atherosclerosis\(^{49-51}\)) thought to underlie the increased risk of vascular disease may also contribute to the pathophysiological features of AMD.\(^{36-39}\) The trial findings reported herein are the strongest evidence to date in support of a possible beneficial effect of folic acid and B vitamin supplements in AMD prevention. Moreover, because these findings apply to the early stages of AMD development (most cases were characterized by a combination of drusen and RPE changes) in persons with-
out a prior diagnosis of AMD, they appear to represent the first identified means, other than avoidance of cigarette smoking, of reducing risks of AMD in persons at usual risk. From a public health perspective, this is particularly important because persons with early AMD are at increased risk of developing advanced AMD, the leading cause of severe, irreversible vision loss in older Americans.

Whether the reduced risk of AMD observed in WAFACS is due to lowering of homocysteine levels by the combination treatment or is independent of lowered homocysteine levels is an important question to be investigated. We examined the impact of the intervention on homocysteine levels in a substudy of 300 WAFACS participants (150 in each treatment group) who had blood samples collected at study entry in 1993 through 1995, and again at study completion in 2005. Details of the substudy are presented elsewhere.42 In short, the geometric mean plasma homocysteine level was decreased by 18.5% (95% CI, 12.5%-24.1% [P < .001]) in the active arm compared with the placebo arm, a difference of 0.31 mg/L (95% CI, 0.21-0.40 mg/L). These substudy findings indicate that the reduced risk of AMD we observed in the combination treatment group may have been due, at least in part, to lowering of homocysteine levels. However, a treatment benefit independent of lowering homocysteine levels is also possible. Plausible mechanisms include a direct antioxidant effect of folic acid and B vitamin supplements and enhancement of endothelial nitric oxide levels in the cho-

### Table 2. Risk for Diagnosis of Visually Significant AMD According to Combination Treatment Assignment, as Modified by Other Risk Factors

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. With AMD/No. of Participants</th>
<th>Combination Treatmenta</th>
<th>Placebo b</th>
<th>RRb (95% CI)</th>
<th>P Valuec</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td>(n=2607)</td>
<td>(n=2598)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40-54</td>
<td>0/574</td>
<td>2/573</td>
<td>NA</td>
<td></td>
<td>.24</td>
</tr>
<tr>
<td>55-64</td>
<td>4/968</td>
<td>9/942</td>
<td>0.42 (0.13-1.38)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥65</td>
<td>22/1065</td>
<td>33/1083</td>
<td>0.67 (0.39-1.15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.47</td>
</tr>
<tr>
<td>Current</td>
<td>2/296</td>
<td>7/318</td>
<td>0.32 (0.07-1.55)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Past only</td>
<td>12/1137</td>
<td>19/1170</td>
<td>0.61 (0.30-1.26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>12/1174</td>
<td>18/1110</td>
<td>0.66 (0.32-1.37)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.54</td>
</tr>
<tr>
<td>Daily</td>
<td>8/866</td>
<td>17/850</td>
<td>0.45 (0.20-1.05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weekly</td>
<td>7/318</td>
<td>5/321</td>
<td>1.33 (0.42-4.21)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rarely/never</td>
<td>11/1423</td>
<td>22/1427</td>
<td>0.50 (0.24-1.04)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.76</td>
</tr>
<tr>
<td>&lt;25.0</td>
<td>8/586</td>
<td>11/528</td>
<td>0.63 (0.25-1.58)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25.0-29.9</td>
<td>9/727</td>
<td>16/767</td>
<td>0.62 (0.27-1.40)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥30.0</td>
<td>9/1294</td>
<td>17/1383</td>
<td>0.53 (0.24-1.19)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.16</td>
</tr>
<tr>
<td>Yes</td>
<td>20/2258</td>
<td>39/2227</td>
<td>0.50 (0.29-0.86)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>6/349</td>
<td>5/371</td>
<td>1.21 (0.37-3.99)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.97</td>
</tr>
<tr>
<td>Yes</td>
<td>20/2023</td>
<td>34/2046</td>
<td>0.59 (0.34-1.02)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>6/584</td>
<td>10/552</td>
<td>0.70 (0.25-1.97)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.19</td>
</tr>
<tr>
<td>Yes</td>
<td>1/554</td>
<td>7/560</td>
<td>0.14 (0.02-1.12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>25/2093</td>
<td>37/2038</td>
<td>0.85 (0.39-1.99)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior CVD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.57</td>
</tr>
<tr>
<td>Yes</td>
<td>21/1678</td>
<td>33/1627</td>
<td>0.64 (0.37-1.09)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>5/929</td>
<td>11/971</td>
<td>0.45 (0.16-1.30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current HT use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.92</td>
</tr>
<tr>
<td>Yes</td>
<td>12/1274</td>
<td>21/1280</td>
<td>0.60 (0.29-1.22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>14/1102</td>
<td>23/1096</td>
<td>0.57 (0.29-1.11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current use of multivitamin supplements</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.92</td>
</tr>
<tr>
<td>Yes</td>
<td>6/587</td>
<td>9/599</td>
<td>0.72 (0.26-2.03)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>20/2020</td>
<td>35/1997</td>
<td>0.56 (0.32-0.97)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin use in past mo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.30</td>
</tr>
<tr>
<td>Yes</td>
<td>18/1626</td>
<td>36/1614</td>
<td>0.51 (0.29-0.90)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>8/980</td>
<td>8/984</td>
<td>0.91 (0.34-2.44)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AMD, age-related macular degeneration; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CI, confidence interval; CVD, cardiovascular disease; HT, hormone therapy; NA, not applicable; RR, replacement risk.

* Indicates folic acid (2.5 mg/d), pyridoxine hydrochloride (vitamin B6) (50 mg/d), and cyanocobalamin (vitamin B12) (1 mg/d).

* Adjusted for age and vitamin C, vitamin E, and beta carotene treatment assignment.

* Calculated by means of a test of interaction.

* Analysis was restricted to postmenopausal women.

* Information on current use of multivitamins was missing for 2 participants in the placebo group.

* Information on aspirin use in the past month was missing for 1 participant in the combination treatment group.

©2009 American Medical Association. All rights reserved.
roidal vasculature, with an associated increase in vascular reactivity. Further study is required to distinguish between these and other possibilities.

Our findings for AMD are in sharp contrast to the null findings for CVD observed in the WAFACS and other completed trials to lower homocysteine levels in persons with preexisting vascular disease, despite substantial lowering of homocysteine concentrations by study treatment in those trials. Although our findings could be due to chance and need to be confirmed in other populations, it may be worthwhile to consider whether the discordant findings for AMD and CVD reflect important differences between the choroidal and systemic vasculature with respect to responsiveness to the lowering of homocysteine levels. Age-related macular degeneration is a disease that likely involves damage to the small vessels of the choroid, and some evidence suggests that homocysteine may be a more potent risk factor for small-vessel disease than for large vessel disease. If so, small-vessel diseases such as AMD and perhaps some subtypes of stroke (eg, lacunar brain infarcts and cerebral white matter lesions) may be more amenable to benefit from lowering homocysteine concentrations. A recent meta-analysis of completed trials of therapy to lower homocysteine levels indicated that folic acid supplementation had little effect on CVD (pooled RR, 0.95; 95% CI, 0.88-1.03) or coronary heart disease (1.04; 0.92-1.17), but was associated with a nonsignificant 14% reduced risk for total stroke (0.86; 0.71-1.04). Further detailed analyses of etiologic subtypes of stroke in these trials may suggest a beneficial effect of folic acid supplementation that is observable primarily in diseases of the small vessels.

In summary, daily supplementation with folic acid, pyridoxine, and cyanocobalamin during an average of 7.3 years of follow-up reduced the risk of AMD in women at increased risk of vascular disease. Because there are currently no recognized means to prevent the early stages of AMD development other than avoidance of cigarette smoking, these findings could have important clinical and public health implications and need to be confirmed in other populations of men and women.

Accepted for Publication: September 26, 2008.
Correspondence: William G. Christen, ScD, Division of Preventive Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, 900 Commonwealth Ave E, Boston, MA 02215-1204 (wchristen@rics.bwh.harvard.edu).

Author Contributions: Dr Christen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Manson. Acquisition of data: Christen and Manson. Analysis and interpretation of data: Christen, Glynn, Chew, Albert, and Manson. Drafting of the manuscript: Christen. Critical revision of the manuscript for important intellectual content: Glynn, Chew, Albert, and Manson. Statistical analysis: Glynn. Obtained funding: Christen and Manson. Administrative, technical, and material support: Christen, Albert, and Manson. Study supervision: Christen and Manson.

Financial Disclosure: Dr Christen has received research funding support from the National Institutes of Health, Harvard University (Clinical Nutrition Research Center), and DSM Nutritional Products, Inc (Roche). Dr Glynn has received support from grants to the Brigham and Women's Hospital from AstraZeneca, Bristol-Meyers Squibb Company, Merck and Company, Inc, and Novartis. Dr Manson has received research funding support from the National Institutes of Health and research support for study pills and/or packaging from BASF Corporation and Cognis Corporation.

Funding/Support: This study was supported by grants HL 46959 from the National Heart, Lung, and Blood Institute and EY 06633 from the National Eye Institute. Vitamin E and its placebo were provided by Cognis Corporation. All other agents and their placebos were provided by BASF Corporation.

Role of the Sponsor: Cognis Corporation and BASF Corporation did not participate in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.

Additional Contributions: We are indebted to the 5442 participants in the Women's Antioxidant and Folic Acid Cardiovascular Study for their dedicated and conscientious collaboration; to the entire staff of the Women's Antioxidant and Folic Acid Cardiovascular Study, including Marilyn Chown, MPH, Elaine Zaharris, BA, Ellie Danielson, MIA, Margareta Haabourg, Felicia Zangi, Shamiklah Curry, Tony Laurinaitis, Geneva McNair, Philomena Quinn, Harriet Samuelson, MA, Ara Sarkissian, MM, Jean MacFadyen, BA, and Martin Van Denburgh, BA.

REFERENCES

12. Christen WG, Glynn RJ, Manson JE, Ayan UA, Buring JE: A prospective study of...


