Appendix A
Acknowledgments

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We gratefully acknowledge the following individuals who reviewed the initial draft of this report and provided us with constructive feedback. Acknowledgments are made with the explicit statement that this does not constitute endorsement of the report.

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Appendix B

Search Methodology

SEARCH #1 (PERFORMED 11/16/01)

DATABASES SEARCHED/TIME PERIOD COVERED:

MEDLINE	1966-2001/Dec W2
MANTIS	1880-2001/Aug
Allied & Complementary Medicine	1984-2001/Dec
Cancerlit	1975-2001/Oct
CAB HEALTH	1983-2001/Oct
TGG Health&Wellness DB	1976-2001/Nov W1
Biosis Previews	1969-2001/Nov W2
EMBASE	1974-2001/Nov W2
Social SciSearch	1972-2001/Nov W3
SciSearch Cited Ref Sci	1990-2001/Nov W3
SciSearch Cited Ref Sci	1974-1989/Dec
ELSEVIER BIOBASE	1994-2001/Nov W2

SEARCH STRATEGY:
ubiquinone OR ubidecarenone OR coenzyme q10 OR co-enzyme q10 OR coenzyme q 10 OR co-enzyme q 10 OR coenzyme q-10 OR co-enzyme q-10

AND

cardiovascular diseases(exploded) from Medline,CancerLit
OR cardiovascular disease(exploded) from EMBASE
OR cardiovascular disease* OR coronary artery disease*
OR coronary atherosclerosis OR heart disease*
OR congestive heart failure OR myocardial OR coronary ischemia
OR acute coronary syndrome OR coronary plaque OR heart plaque
OR arter* plaque

AND

(prevention OR preventive OR therapy OR therapeutic OR treatment) in title,subject heading fields

AND

Human

NOT

(cell OR cells) in subject heading field

TOTAL NUMBER OF ITEMS RETRIEVED: 582

SEARCH #2a (PERFORMED 11/27/01)

DATABASES SEARCHED/TIME PERIOD COVERED:

MEDLINE	1966-2001/Dec W4
MANTIS	1880-2001/Aug
Allied & Complementary Medicine	1984-2001/Dec
Cancerlit	1975-2001/Oct
CAB HEALTH	1983-2001/Oct
TGG Health&Wellness DB	1976-2001/Nov W2
Biosis Previews	1969-2001/Nov W3
EMBASE	1974-2001/Nov W3
Social SciSearch	1972-2001/Nov W4
SciSearch Cited Ref Sci	1990-2001/Nov W4
SciSearch Cited Ref Sci	1974-1989/Dec
ELSEVIER BIOBASE	1994-2001/Nov W4

SEARCH STRATEGY:
ascorbic acid(exploded)from Medline, Embase OR ascorbic acid OR
dehydroascorbic acid* OR ascorbate OR vitamin c OR antiscorbutic vitamin*
OR cevitamic acid*

AND

cardiovascular diseases(exploded) from Medline,CancerLit
OR cardiovascular disease(exploded) from EMBASE
OR cardiovascular disease* OR coronary artery disease*
OR coronary atherosclerosis OR heart disease*
OR congestive heart failure OR myocardial OR coronary ischemia
OR acute coronary syndrome OR coronary plaque OR heart plaque
OR arter* plaque

AND

(prevention OR preventive OR therapy OR therapeutic OR treatment) in title,subject heading fields

AND

human

NOT

(cell OR cells) in subject heading field

TOTAL NUMBER OF ITEMS RETRIEVED: 2228 [NOTE: NOT ALL DUPLICATE RECORDS WERE DELETED FROM THESE RESULTS – RS]

SEARCH #2b (PERFORMED 11/7/01)

DATABASES SEARCHED:

Cochrane Library

SEARCH STRATEGY:

vitamin c OR ascorbic acid OR ascorbate OR antiscorbutic vitamin OR cevitamic acid OR dehydroascorbic acid

AND

cardiovascular diseases(exploded)

TOTAL NUMBER OF ITEMS RETRIEVED:

The Cochrane Database of Systematic Reviews
Complete reviews - 11

Database of Abstracts of Reviews of Effectiveness
Abstracts of quality assessed systematic reviews - 3

The Cochrane Controlled Trials Register (CENTRAL/CCTR)
References - 155

SEARCH #3a (PERFORMED 12/4/01)

DATABASES SEARCHED/TIME PERIOD COVERED:

MEDLINE	1966-2001/Dec W5
MANTIS	1880-2001/Aug
Allied & Complementary Medicine	1984-2001/Jan
Cancerlit	1975-2001/Oct
CAB HEALTH	1983-2001/Oct
TGG Health&Wellness DB	1976-2001/Nov W3
Biosis Previews	1969-2001/Nov W4
EMBASE	1974-2001/Nov W4
Social SciSearch	1972-2001/Dec W1
SciSearch Cited Ref Sci	1990-2001/Dec W1
SciSearch Cited Ref Sci	1974-1989/Dec
ELSEVIER BIOBASE	1994-2001/Dec W1

SEARCH STRATEGY:
vitamin e (exploded) from Medline OR vitamin e OR alpha tocopherol* OR d1 alpha tocopherol* OR d alpha tocopherol OR rrr alpha tocopherol* OR all rac alpha tocopherol*

AND

cardiovascular diseases(exploded) from Medline,CancerLit
OR cardiovascular disease(exploded) from EMBASE
OR cardiovascular disease* OR coronary artery disease*
OR coronary atherosclerosis OR heart disease*
OR congestive heart failure OR myocardial OR coronary ischemia
OR acute coronary syndrome OR coronary plaque OR heart plaque
OR arter* plaque

AND

(prevention OR preventive OR therapy OR therapeutic OR treatment) in title,subject heading fields

AND

human

TOTAL NUMBER OF ITEMS RETRIEVED: 3578

SEARCH #3b (PERFORMED 12/19/01)

DATABASES SEARCHED/TIME PERIOD COVERED:

Cochrane Library	1922-2001

SEARCH STRATEGY:
vitamin-e

AND

cardiovascular diseases(exploded) OR coronary
OR heart OR myocardial

TOTAL NUMBER OF ITEMS RETRIEVED:

The Cochrane Database of Systematic Reviews - Complete reviews: 1

Database of Abstracts of Reviews of Effectiveness
Abstracts of quality assessed systematic reviews: 1
Other reviews: bibliographic details only: 3

The Cochrane Controlled Trials Register (CENTRAL/CCTR) – References: 187

SEARCH #4 (PERFORMED 1/25/02)

DATABASES SEARCHED/TIME PERIOD COVERED:

MEDLINE	1966-2002/JAN W3
MANTIS	1880-2001/Oct
Allied & Complementary Medicine	1984-2002/Feb
Cancerlit	1975-2001/Oct
CAB HEALTH	1983-2001/Dec
TGG Health&Wellness DB	1976-2002/Jan W1
Biosis Previews	1969-2002/Jan W3
EMBASE	1974-2002/Jan W3
Social SciSearch	1972-2002/Jan W4
SciSearch Cited Ref Sci	1990-2002/Jan W4
SciSearch Cited Ref Sci	1974-1989/Dec
ELSEVIER BIOBASE	1994-2002/Jan W3

SEARCH STRATEGY:
ubidecarenon* OR isoprostane* OR f2 isoprostane*

AND

cardiovascular diseases (exploded) from Medline, CancerLit, Embase OR cardiovascular disease* OR coronary artery disease* OR coronary atherosclerosis OR heart disease* OR congestive heart failure OR myocardial OR coronary ischemia OR acute coronary syndrome OR coronary plaque OR heart plaque OR arter* plaque

AND

Human

NOT

(coenzyme OR co enzyme) within 2 words of (q10 or q 10)

TOTAL NUMBER OF ITEMS RETRIEVED: 503

SEARCH #5 PERFORMED 11/7/01

DATABASE SEARCHED:

Cochrane Library

SEARCH STRATEGY:

coenzyme q10 or coenzyme q 10 OR co enzyme q10 OR co enzyme q 10 OR co q10 OR co q 10 OR ubiquinone

TOTAL NUMBER OF ITEMS RETRIEVED:

The Cochrane Database of Systematic Reviews - Complete reviews - 1
The Cochrane Controlled Trials Register (CENTRAL/CCTR) References - 110

Appendix C

Article# **Antioxidant Screener** **RAND EPC Alternative Medicine**

Reviewers: _____ mm/dd/yy
_____ mm/dd/yy

Assigned on:

[article author, title, journal, date, vol, pages]

1. Data Source: **Circle One**
   - Article 1
   - Abstract of article 2
   - Conference proceeding 3
   - Other (Specify_____) 4

2. What topic does the article study: **Check all that apply**
   - Vitamin C .....
   - Vitamin E .....
   - Co-Enzyme Q10 .....
   - Other (Specify_____) .. (STOP)
   - Unclear .....

3. Condition(s) and/or disease(s) studied in article: **Check all that apply**
   - Cancer .....
   - Cardiovascular Disease .....
   - No condition/disease ..... (STOP)
   - Other (Specify_____) .... (STOP)
   - Unclear .....

4. Subject Population: **Check all that apply**
   - Human .....
   - In vitro / In vivo ..... (STOP)
   - Animal ..... (STOP)
   - Other (Specify_____) .... (STOP)
   - Unclear .....

5. Article Type: **Check all that apply**
   - Historical/Descriptive/System/Bkgrd .....
   - Review/Meta-analysis .....
   - Pharmacological .....
   - Clinical Study
     - Trial .....
     - Cohort .....
     - Other clinical study .....
   - Other (Specify_____) ....
   - Unclear .....

6. How is the intervention being used in the study? **Circle One**
   - Treatment 1
   - Primary prevention 2
   - Secondary prevention 3
   - Adjunct to conventional treatment 4
   - Other (Specify_____) .. 5
   - Unclear 6

7. Language of Article: **Circle One**
   - English 1
   - Foreign 2

NOTES:

Abstract:

RAND EPC, CAM Project

Quality Review Form, Topic = ANTIOXIDANT

Article ID:_____ Reviewer:_____

First Author: _____
(Last Name Only)

Study Number: ___of____Description:_____
(Enter '1of 1' if only one) (if more than one study)

1. Design: (circle one)
   - RCT 1
   - CCT 2
   - Other ..... 3 **(STOP)**

(If not RCT or CCT, change study design on cover sheet and STOP)

2. What topic(s) does the study report on? ..... (check all that apply)
   - Vitamin C ..... ❑
   - Vitamin E ..... ❑
   - Co-Q10 ..... ❑
   - None of the above ..... ❑ **(STOP)**

2. What condition(s) does the study report on? (circle one)
   - Cardiovascular 1
   - Cancer 2
   - Both 3
   - None ..... 4 **(STOP)**

3. Is the study described as randomized? (circle one)
   - Yes 1
   - No 2

4. If the study was randomized, was method of randomization appropriate? (circle one)
   - Yes 1
   - No 2
   - Method not described 8
   - Not applicable 9

5. Is the study described as: (circle one)
   - Double blind 1
   - Single blind, patient 2
   - Single blind, outcome assessment 3
   - Open 4
   - Blinding not described 8
   - Not applicable 9

6. If reported, was the method of double blinding appropriate? (circle one)
   - Yes 1
   - No 2
   - Double blinding method not described 8
   - Not applicable 9

7. If study was randomized, did the method of randomization provide for concealment of allocation? (circle one)
   - Yes 1
   - No 2
   - Concealment not described 8
   - Not applicable 9

8. Are withdrawals (W) and dropouts (D) described? (circle one)
   - Yes, reason described for **all** W and D 1
   - Yes, reason described for **some** W and D 2
   - Not described 8
   - Not applicable 9

9. Is this a cross-over study design? (circle one)
   - Yes 1
   - No 2
   - Not described 8

RAND EPC, CAM Project
Quality Review Form, Topic = ANTIOXIDANT

10. Does the study population include a purposefully selected group of individuals chosen because they have any of the following characteristics? (check all that apply)

Race:
- African-American ..... ❑ (01)
- Asian ..... ❑ (02)
- Hispanic ..... ❑ (03)

Gender:
- Male ..... ❑ (04)
- Female ..... ❑ (05)

Age:
- Children (under 18) ..... ❑ (06)
- Elderly (over 65) ..... ❑ (07)

Miscellaneous:
- Smokers ..... ❑ (08)

Other:
- (Enter code: ____ ____, ____ ____, ____ ___, ____ ____, ____ ____)

None of the above ..... ❑ (97)

11. Does the study population include a purposefully selected group of individuals chosen because they have any of the following comorbidities? (enter code or circle)

Code: ____ ____, ____ ____, ____ ___, ____ ____, ____ ____

Not applicable 99

12. Does the study population include a purposefully selected group of individuals chosen because they have any of the following predisposing factors? (enter code or circle)

Code: ____ ____, ____ ____, ____ ___, ____ ____, ____ ____

Not applicable 99

13. If this study is from a larger trial, please note the name of original trial. (circle one or enter code)

- ADMT ..... ❑ (01)
- ATBC ..... ❑ (02)
- CGPPP ..... ❑ (03)
- CHAOS ..... ❑ (04)
- GISSI/GIZZI ..... ❑ (05)
- HOPE ..... ❑ (06)
- MRC/BHF ..... ❑ (07)
- PHS II ..... ❑ (08)
- SPACE ..... ❑ (09)
- SU.VI.MAX ..... ❑ (10)
- WHI ..... ❑ (11)
- WHS ..... ❑ (12)

Code: ____ ____

Not from a larger trial ..... ❑ (99)

Patient Characteristics – CARDIOVASCULAR

14.…What type of cardiovascular disease did the study report on?
(check all that apply and/or add code)

CAD ..... (01)
CVA/TIA..... (02)
PVD..... (03)
CHF ..... (04)
Angina ..... (05)

Code: ____ ____

____ ____

____ ____

____ ____

Not Applicable..... (99)

15.…What was the severity of the disease?

Enter code: ____ ____
(enter 99 if not applicable)

Patient Characteristics – CANCER

16. What type of cancer did the study report on?
(check all that apply and/or add code)

Breast..... (01)
Lung ..... (02)
Prostate ..... (03)
Oral..... (04)
Cervix ..... (05)
Gastric ..... (06)
Colon ..... (07)

Code: ____ ____

____ ____

____ ____

____ ____

Not Applicable 99

17. What was the severity of the disease? (check all that apply and/or add code)

Pre-cancerous ..... (01)
Localized ..... (02)
Metastatic ..... (03)

Other code: ____ ____

Not Applicable 99

RAND EPC, CAM Project

Quality Review Form, Topic = ANTIOXIDANT

If the study has a control/usual care arm, enter that data in arm 1.
Otherwise, enter data for the groups in order of first mention.

Arm 1 of Description:

18. What type of arm is this? (circle one)
    - Placebo 1
    - Usual care 2
    - Primary Antioxidant 3
    - Other active treatment 4

19. What was the sample size in this arm?

___ ___ ___ , ___ ___ ___ Entering

___ ___ ___ , ___ ___ ___ Completing

(Enter 999,999 if not reported.)

---

20. Intervention:

Intervention	Daily Dose	Units		Route of administration	Duration	Units
1 _____	_____	_____	taken	_____	_____	_____
2 _____	_____	_____	taken	_____	_____	_____
3 _____	_____	_____	taken	_____	_____	_____
4 _____	_____	_____	taken	_____	_____	_____
Enter code	Enter a number	1. µg 2. mg 3. gm 4. IU 8. ND 9. NA		1. PO 2. IV 8. ND 9. NA	Enter a number 998. ND 999. NA	1. Hour 2. Day 3. Week 4. Month 5. Year 6. Mean Month 7. Median Month 8. Mean Year 9. Median Year 10. Maximum Month 11. Minimum Month 12. Maximum Year 13. Minimum Year 98. ND 99. NA

RAND EPC, CAM Project
Quality Review Form, Topic = ANTIOXIDANT

If the study has a control/usual care arm, enter that data in arm 1.
Otherwise, enter data for the groups in order of first mention.

Arm 2 of Description:

18. What type of arm is this? (circle one)
    - Placebo 1
    - Usual care 2
    - Primary Antioxidant 3
    - Other active treatment 4

19. What was the sample size in this arm?

___ ___ ___ , ___ ___ ___ Entering ___ ___ ___ , ___ ___ ___ Completing

(Enter 999,999 if not reported.)

20. Intervention:

Intervention	Daily Dose	Units		Route of administration	Duration	Units
1 _____	_____	_____	taken	_____	_____	_____
2 _____	_____	_____	taken	_____	_____	_____
3 _____	_____	_____	taken	_____	_____	_____
4 _____	_____	_____	taken	_____	_____	_____
Enter code	Enter a number	1. µg 2. mg 3. gm 4. IU 8. ND 9. NA		1. PO 2. IV 8. ND 9. NA	Enter a number 998. ND 999. NA	1. Hour 2. Day 3. Week 4. Month 5. Year 6. Mean Month 7. Median Month 8. Mean Year 9. Median Year 10. Maximum Month 11. Minimum Month 12. Maximum Year 13. Minimum Year 98. ND 99. NA

RAND EPC, CAM Project
Quality Review Form, Topic = ANTIOXIDANT

If the study has a control/usual care arm, enter that data in arm 1.
Otherwise, enter data for the groups in order of first mention.

Arm 3 of Description:

18. What type of arm is this? (circle one)
    - Placebo.....1
    - Usual care 2
    - Primary Antioxidant 3
    - Other active treatment.....4

19. What was the sample size in this arm?

___ ___ ___ , ___ ___ ___ Entering ___ ___ ___ , ___ ___ ___ Completing

(Enter 999,999 if not reported.)

---

20. Intervention:

Intervention	Daily Dose	Units		Route of administration	Duration	Units
1 _____	_____	_____	taken	_____	_____	_____
2 _____	_____	_____	taken	_____	_____	_____
3 _____	_____	_____	taken	_____	_____	_____
4 _____	_____	_____	taken	_____	_____	_____
Enter code	Enter a number	1. µg 2. mg 3. gm 4. IU 8. ND 9. NA		1. PO 2. IV 8. ND 9. NA	Enter a number 998. ND 999. NA	1. Hour 2. Day 3. Week 4. Month 5. Year 6. Mean Month 7. Median Month 8. Mean Year 9. Median Year 10. Maximum Month 11. Minimum Month 12. Maximum Year 13. Minimum Year 98. ND 99. NA

RAND EPC, CAM Project
Quality Review Form, Topic = ANTIOXIDANT

If the study has a control/usual care arm, enter that data in arm 1.
Otherwise, enter data for the groups in order of first mention.

Arm 4 of Description:

18. What type of arm is this? (circle one)
    - Placebo 1
    - Usual care 2
    - Primary Antioxidant 3
    - Other active treatment 4

19. What was the sample size in this arm?

___ ___ ___ , ___ ___ ___ Entering ___ ___ ___ , ___ ___ ___ Completing

(Enter 999,999 if not reported.)

20. Intervention:

Intervention	Daily Dose	Units		Route of administration	Duration	Units	
1 _____	_____	_____	taken	_____	_____	_____	
2 _____	_____	_____	taken	_____	_____	_____	
3 _____	_____	_____	taken	_____	_____	_____	
4 _____	_____	_____	taken	_____	_____	_____	
Enter code	Enter a number	1. µg		1. PO	Enter a number	1. Hour	8. Mean Year
		2. mg		2. IV		2. Day	9. Median Year
	998. ND	3. gm		8. ND	998. ND	3. Week	10. Maximum Month
	999. NA	4. IU		9. NA	999. NA	4. Month	11. Minimum Month
		8. ND				5. Year	12. Maximum Year
		9. NA				6. Mean Month	13. Minimum Year
						7. Median Month	98. ND
							99. NA

RAND EPC, CAM Project
Quality Review Form, Topic = ANTIOXIDANT

Outcomes

21. Type of outcomes measured:

Enter the code for each outcome measured.
____ ____
____ ____
____ ____
____ ____
____ ____
____ ____
____ ____
____ ____
____ ____
____ ____
____ ____
____ ____

Evaluation

22. When, relative to the start of the intervention, were outcomes reported?

Enter the number and letters in the appropriate box

	Number	Unit
1st follow-up		
2nd follow-up		
3rd follow-up		
4th follow-up		
5th follow-up		
6th follow-up		
Additional follow-ups:		

Use the following abbreviations for units:

MI	minute
HR	hour
DY	day
WK	week
MO	month
YR	year
YRMN	mean for year
YRME	median for year
YRMX	maximum for year
YRMI	minimum for year
MOMN	mean for month
MOME	median for month
MOMX	maximum for month
MOMI	minimum for month
ND	not described
NA	not applicable

23. Is there a sub-group analysis? (circle one)

Yes 1
No 2

If yes, code

_____ _____ _____ _____

_____ _____ _____ _____

_____ _____ _____ _____

RAND EPC, CAM Project

Quality Review Form, Topic = ANTIOXIDANT

Article ID:_____ Reviewer:_____

First Author: _____
(Last Name Only)

Study Number: ___of____Description:_____
(Enter '1of 1' if only one) (if more than one study)

1. Design: (circle one)
   - RCT 1
   - CCT 2
   - Other ..... 3 **(STOP)**

(If not RCT or CCT, change study design on cover sheet and STOP)

2. What topic(s) does the study report on? ..... (check all that apply)
   - Vitamin C ..... ❑
   - Vitamin E ..... ❑
   - Co-Q10 ..... ❑
   - None of the above ..... ❑ **(STOP)**

2. What condition(s) does the study report on? (circle one)
   - Cardiovascular 1
   - Cancer 2
   - Both 3
   - None ..... 4 **(STOP)**

3. Is the study described as randomized? (circle one)
   - Yes 1
   - No 2

4. If the study was randomized, was method of randomization appropriate? (circle one)
   - Yes 1
   - No 2
   - Method not described 8
   - Not applicable 9

5. Is the study described as: (circle one)
   - Double blind 1
   - Single blind, patient 2
   - Single blind, outcome assessment 3
   - Open 4
   - Blinding not described 8
   - Not applicable 9

6. If reported, was the method of double blinding appropriate? (circle one)
   - Yes 1
   - No 2
   - Double blinding method not described 8
   - Not applicable 9

7. If study was randomized, did the method of randomization provide for concealment of allocation? (circle one)
   - Yes 1
   - No 2
   - Concealment not described 8
   - Not applicable 9

8. Are withdrawals (W) and dropouts (D) described? (circle one)
   - Yes, reason described for **all** W and D 1
   - Yes, reason described for **some** W and D 2
   - Not described 8
   - Not applicable 9

9. Is this a cross-over study design? (circle one)
   - Yes 1
   - No 2
   - Not described 8

RAND EPC, CAM Project
Quality Review Form, Topic = ANTIOXIDANT

10. Does the study population include a purposefully selected group of individuals chosen because they have any of the following characteristics? (check all that apply)

Race:
- African-American ..... ❑ (01)
- Asian ..... ❑ (02)
- Hispanic ..... ❑ (03)

Gender:
- Male ..... ❑ (04)
- Female ..... ❑ (05)

Age:
- Children (under 18) ..... ❑ (06)
- Elderly (over 65) ..... ❑ (07)

Miscellaneous:
- Smokers ..... ❑ (08)

Other:
- (Enter code: ____ ____, ____ ____, ____ ___, ____ ____, ____ ____)

None of the above ..... ❑ (97)

11. Does the study population include a purposefully selected group of individuals chosen because they have any of the following comorbidities? (enter code or circle)

Code: ____ ____, ____ ____, ____ ___, ____ ____, ____ ____

Not applicable 99

12. Does the study population include a purposefully selected group of individuals chosen because they have any of the following predisposing factors? (enter code or circle)

Code: ____ ____, ____ ____, ____ ___, ____ ____, ____ ____

Not applicable 99

13. If this study is from a larger trial, please note the name of original trial. (circle one or enter code)

- ADMT ..... ❑ (01)
- ATBC ..... ❑ (02)
- CGPPP ..... ❑ (03)
- CHAOS ..... ❑ (04)
- GISSI/GIZZI ..... ❑ (05)
- HOPE ..... ❑ (06)
- MRC/BHF ..... ❑ (07)
- PHS II ..... ❑ (08)
- SPACE ..... ❑ (09)
- SU.VI.MAX ..... ❑ (10)
- WHI ..... ❑ (11)
- WHS ..... ❑ (12)

Code: ____ ____

Not from a larger trial ..... ❑ (99)

Patient Characteristics – CARDIOVASCULAR

14.…What type of cardiovascular disease did the study report on?
(check all that apply and/or add code)

CAD ..... (01)
CVA/TIA..... (02)
PVD..... (03)
CHF ..... (04)
Angina ..... (05)

Code: ____ ____

____ ____

____ ____

____ ____

Not Applicable..... (99)

15.…What was the severity of the disease?

Enter code: ____ ____
(enter 99 if not applicable)

Patient Characteristics – CANCER

16. What type of cancer did the study report on?
(check all that apply and/or add code)

Breast..... (01)
Lung ..... (02)
Prostate ..... (03)
Oral..... (04)
Cervix ..... (05)
Gastric ..... (06)
Colon ..... (07)

Code: ____ ____

____ ____

____ ____

____ ____

Not Applicable 99

17. What was the severity of the disease? (check all that apply and/or add code)

Pre-cancerous ..... (01)
Localized ..... (02)
Metastatic ..... (03)

Other code: ____ ____

Not Applicable 99

RAND EPC, CAM Project

Quality Review Form, Topic = ANTIOXIDANT

If the study has a control/usual care arm, enter that data in arm 1.
Otherwise, enter data for the groups in order of first mention.

Arm 1 of Description:

18. What type of arm is this? (circle one)
    - Placebo 1
    - Usual care 2
    - Primary Antioxidant 3
    - Other active treatment 4

19. What was the sample size in this arm?

___ ___ ___ , ___ ___ ___ Entering

___ ___ ___ , ___ ___ ___ Completing

(Enter 999,999 if not reported.)

---

20. Intervention:

Intervention	Daily Dose	Units		Route of administration	Duration	Units
1 _____	_____	_____	taken	_____	_____	_____
2 _____	_____	_____	taken	_____	_____	_____
3 _____	_____	_____	taken	_____	_____	_____
4 _____	_____	_____	taken	_____	_____	_____
Enter code	Enter a number	1. µg 2. mg 3. gm 4. IU 8. ND 9. NA		1. PO 2. IV 8. ND 9. NA	Enter a number 998. ND 999. NA	1. Hour 2. Day 3. Week 4. Month 5. Year 6. Mean Month 7. Median Month 8. Mean Year 9. Median Year 10. Maximum Month 11. Minimum Month 12. Maximum Year 13. Minimum Year 98. ND 99. NA

RAND EPC, CAM Project
Quality Review Form, Topic = ANTIOXIDANT

If the study has a control/usual care arm, enter that data in arm 1.
Otherwise, enter data for the groups in order of first mention.

Arm 2 of Description:

18. What type of arm is this? (circle one)
    - Placebo 1
    - Usual care 2
    - Primary Antioxidant 3
    - Other active treatment 4

19. What was the sample size in this arm?

___ ___ ___ , ___ ___ ___ Entering ___ ___ ___ , ___ ___ ___ Completing

(Enter 999,999 if not reported.)

20. Intervention:

Intervention	Daily Dose	Units		Route of administration	Duration	Units
1 _____	_____	_____	taken	_____	_____	_____
2 _____	_____	_____	taken	_____	_____	_____
3 _____	_____	_____	taken	_____	_____	_____
4 _____	_____	_____	taken	_____	_____	_____
Enter code	Enter a number	1. µg 2. mg 3. gm 4. IU 8. ND 9. NA		1. PO 2. IV 8. ND 9. NA	Enter a number 998. ND 999. NA	1. Hour 2. Day 3. Week 4. Month 5. Year 6. Mean Month 7. Median Month 8. Mean Year 9. Median Year 10. Maximum Month 11. Minimum Month 12. Maximum Year 13. Minimum Year 98. ND 99. NA

RAND EPC, CAM Project
Quality Review Form, Topic = ANTIOXIDANT

If the study has a control/usual care arm, enter that data in arm 1.
Otherwise, enter data for the groups in order of first mention.

Arm 3 of Description:

18. What type of arm is this? (circle one)
    - Placebo.....1
    - Usual care 2
    - Primary Antioxidant 3
    - Other active treatment.....4

19. What was the sample size in this arm?

___ ___ ___ , ___ ___ ___ Entering ___ ___ ___ , ___ ___ ___ Completing

(Enter 999,999 if not reported.)

---

20. Intervention:

Intervention	Daily Dose	Units		Route of administration	Duration	Units
1 _____	_____	_____	taken	_____	_____	_____
2 _____	_____	_____	taken	_____	_____	_____
3 _____	_____	_____	taken	_____	_____	_____
4 _____	_____	_____	taken	_____	_____	_____
Enter code	Enter a number	1. µg 2. mg 3. gm 4. IU 8. ND 9. NA		1. PO 2. IV 8. ND 9. NA	Enter a number 998. ND 999. NA	1. Hour 2. Day 3. Week 4. Month 5. Year 6. Mean Month 7. Median Month 8. Mean Year 9. Median Year 10. Maximum Month 11. Minimum Month 12. Maximum Year 13. Minimum Year 98. ND 99. NA

RAND EPC, CAM Project
Quality Review Form, Topic = ANTIOXIDANT

If the study has a control/usual care arm, enter that data in arm 1.
Otherwise, enter data for the groups in order of first mention.

Arm 4 of Description:

18. What type of arm is this? (circle one)
    - Placebo 1
    - Usual care 2
    - Primary Antioxidant 3
    - Other active treatment 4

19. What was the sample size in this arm?

___ ___ ___ , ___ ___ ___ Entering ___ ___ ___ , ___ ___ ___ Completing

(Enter 999,999 if not reported.)

20. Intervention:

Intervention	Daily Dose	Units		Route of administration	Duration	Units	
1 _____	_____	_____	taken	_____	_____	_____	
2 _____	_____	_____	taken	_____	_____	_____	
3 _____	_____	_____	taken	_____	_____	_____	
4 _____	_____	_____	taken	_____	_____	_____	
Enter code	Enter a number	1. µg		1. PO	Enter a number	1. Hour	8. Mean Year
		2. mg		2. IV		2. Day	9. Median Year
	998. ND	3. gm		8. ND	998. ND	3. Week	10. Maximum Month
	999. NA	4. IU		9. NA	999. NA	4. Month	11. Minimum Month
		8. ND				5. Year	12. Maximum Year
		9. NA				6. Mean Month	13. Minimum Year
						7. Median Month	98. ND
							99. NA

RAND EPC, CAM Project
Quality Review Form, Topic = ANTIOXIDANT

Outcomes

21. Type of outcomes measured:

Enter the code for each outcome measured.
____ ____
____ ____
____ ____
____ ____
____ ____
____ ____
____ ____
____ ____
____ ____
____ ____
____ ____
____ ____

Evaluation

22. When, relative to the start of the intervention, were outcomes reported?

Enter the number and letters in the appropriate box

	Number	Unit
1st follow-up		
2nd follow-up		
3rd follow-up		
4th follow-up		
5th follow-up		
6th follow-up		
Additional follow-ups:		

Use the following abbreviations for units:

MI	minute
HR	hour
DY	day
WK	week
MO	month
YR	year
YRMN	mean for year
YRME	median for year
YRMX	maximum for year
YRMI	minimum for year
MOMN	mean for month
MOME	median for month
MOMX	maximum for month
MOMI	minimum for month
ND	not described
NA	not applicable

23. Is there a sub-group analysis? (circle one)

Yes 1
No 2

If yes, code

_____ _____ _____ _____

_____ _____ _____ _____

_____ _____ _____ _____

Appendix E

Reviewers' Critique	Authors' Response to Comments
I found the decisions about whether/where to combine/report primary and secondary prevention trials very confusing. Primary prevention trials were not included in the pooled analysis, but were included in the discussion as a reported individual study. Thus, comparisons were made between secondary and primary prevention without explicitly labeling it as such. For example, on p 4 it states that "we did not find evidence in the pooled analysis of smaller trials that vitamin E . . . had a significant effect on all cause mortality. However, a 20% reduction in mortality was reported in the ATBC and Linxian trials . . ." When I first read this I assumed the distinction was being made on the basis of size: by what was seen in smaller trials versus larger trials. But later I realized that the "pooled analysis of smaller trials" included only secondary prevention trials, and ATBC and Linxian are primary prevention trials; thus the distinction was really by type of study.	We have tried to make these distinctions clearer in their revision. The decisions were based on sample size. However, this also had the effect of segregating the primary prevention trials from the secondary prevention trials.
It appears a serious oversight that the definition of antioxidant nutrients and the evaluative criteria necessary for determining antioxidant activity developed by the Institute of Medicine (IOM) Food and Nutrition Board was omitted from the report. Incorporate note into.	Added description of antioxidants and supplements based on IOM and added reference.
Definition of antioxidants. I am not familiar with the reference cited (Ternay, 1997) and wonder whether a more appropriate definition might be the one developed by the IOM (IOM, 2000 – DRIs for Vitamin C, Vitamin E, Selenium, and Carotenoids).	Added description of antioxidants and supplements based on IOM and added reference.
Similarly, the discussion on the Safety of Antioxidant Supplementation ignores the IOM establishment of the DRI Tolerable Upper Intake Levels (UL), their value in clinical and CAM practice, and their implication for future research studies.	Change made to the Introduction section.
First paragraph under "Safety". Suggest qualifying the number of reports (few, several, many?) that have been cited as a true potential interaction from those of documented interactions. 100-800 IU/day are considered safe in short-term; long-term doses >800 IU/day may adversely affect platelet function and doses >1200 IU/day may interfere with vitamin K functions. IOM upper tolerable limit is set at 1000 IU.	We were unclear of the reviewer's distinction between true potential interaction and documented interaction and could not respond to this comment. We did add a sentence about IOM upper tolerable limit.

There is literature suggesting a risk for vitamin E that is not described and that is probably due to increased bleeding. Particularly the ATBC study quoted to provide benefit of vitamin E. In that study vitamin E was associated with increase risk of hemorrhagic strokes by 50% (p=0.07) and fatal subarachnoid bleeding (Leppala JM, et al. Art Thromb Vasc Biol. 2000;20:230). Additionally, an increase in colorectal adenomas was found in ATBC possibly related to bleeding and increase use of colonoscopy (Malila et al. Cancer Epidemiol, Biomarkers and Prevention. 1999;8:489).	Malila article not in this report's bibliography. Change made.
It is clear what was done and I am able to understand what it is you did in order to produce the report. I agree with some but not all of the methods, findings, and conclusions.	No response.
My main issue is that I feel there is too much focus on the few suggestions of benefit, with recommendations that trials be done to confirm these findings, without acknowledgement that in the context of the totality of the evidence, these could well be due to chance. In addition, I still have a philosophic disagreement about such an emphasis on meta-analysis. It just felt disappointing in terms of the amount of information provided to think from the title we'd get a review of all cardiovascular disease and risk factors for three agents, and get only vitamin E, death and MI, and lipids.	We have endeavored to keep the conclusions balanced between the negative and positive findings/results. We have also included in this revision a narrative review of studies on vitamin C and coenzyme Q10.
It was never stated explicitly why supplements of vitamin C, vitamin E, and coenzyme Q10 are considered under the purview of Complementary and Alternative Medicine. If the vitamin C or E were, for example, being obtained by consuming foods rich in these vitamins, they would not, I assume, be considered CAM. Are they considered CAM then, solely because they are being taken as supplements? This should be clarified.	The sponsor (NCCAM) identified for us that the use of these antioxidants as supplements were CAM.
Purpose: Opening sentences. I do not consider the use of antioxidants, notably vitamin C and E, necessarily as CAM treatments. These "nutrients" have been studied for decades and Dietary Reference Intakes (DRIs) have been established for them. Perhaps if you wish to describe them as a CAM modality, include additional text to the effect "in mega-doses" or in doses greatly exceeding the recommended intakes."	See previous reply.
The just-published WAVE trial (*JAMA*, 11/10/02) should be included in the report.	A brief description of results of this study added to results section.
While this reviewer appreciates the requirement to impose a cut-off period in preparing a document such as this, inclusion of the WAVE trial results (Waters et al. *JAMA* 2002;288:2432-40) would further strengthen the null conclusions of this report.	See previous reply.
It would have been useful to know the gender distribution of the participants of the major studies.	We did not collect these data at the time of data extraction and cannot go back and collect it at this time.

I could not find notations on the formulation of agent used in the trial (eg., for vitamin E, was it synthetic or natural source). This would be helpful when you start talking about this issue under Future Research.	Not all of the included reports specify the source of the agent used in the trial. We included in future research that it would be desirable for any new studies to contain this information.
It would be easier to follow if the text and the relevant tables and figures were presented together.	AHRQ requires in their formatting guidelines that we present all tables and figures at the ends of each chapter.
The major strength of this report is its exhaustive and detailed review of the available literature of clinical trials of vitamins C and E and CVD. The major limitation is the absence of a qualitative assessment of this literature, including the distinction between the mechanisms of antioxidant action which may be pertinent to primary prevention of the initiation and progression of CVD lesions versus secondary prevention (maintenance or regression) of established lesions and recurrent event outcomes and death. Within the specific objectives of this report, the available information on vitamin C and coQ was so limited as to make sound conclusions (beyond the need for more research) impossible.	This revision now includes more information about vitamin C and coenzyme Q10. The mechanism of action was not given to us as one of the key questions from the sponsor.
I think it is unfortunate that the investigators chose to limit their analyses to the effects of the 3 antioxidants on mortality, MIs, or lipids. Although this is fine for vitamin E, for which there were an adequate number of studies to address these outcomes, the value of the report is limited with regard to vitamin C and coenzyme Q, for which few (if any) relevant studies were identified. Given the lack of mortality trials, it would have been helpful to review and analyze available data for other outcomes. For example, there have recently been 2 randomized trials of coenzyme Q in patients with heart failure (Khatta et al, Ann Intern Med 2000;132:636-40; Watson et al J Am Coll Cardiol 1999;33:1549-52), both of which provide clinically relevant data.	We included in the revision an expanded description of the vitamin C and coenzyme Q trials in the results section.
The major strengths of this report are that it is comprehensive, thorough, sophisticated in its methodology and statistical approach, and clearly written. The major limitation is that no insights are provided about the current state of knowledge regarding vitamin C and coenzyme Q. Although this limitation is related principally to the lack of published data, it is also in part related to the relatively narrow focus of the report with regard to clinically relevant outcomes.	See previous reply.
The selection of relevant studies of vitamin E in CVD appears appropriate and complete. However, the descriptions of studies with vitamin C and coenzyme Q10 are either very brief or altogether absent. While the report makes clear there are a limited number of such studies, the Results listings in the Table of Contents reveals not a single section is devoted to these two nutrients.	See previous reply.

The title that infers the review will include coenzyme Q10. It is unclear why you did not summarize the results of studies of coenzyme Q10 as used in congestive heart failure, state your opinion of the evidence or lack of evidence, and recommend future studies.	See previous reply.
The title suggests that the report will address the effects of vitamin C, vitamin E and coenzyme Q10 in cardiovascular disease. It does give an excellent overview of our understanding of the antioxidant activities of all three but then concentrates exclusively on the clinical trials of vitamin E. This is not made clear in the structured abstract or introduction.	See previous reply.
Selection Criteria: "Studies were also included if they affected known risk factors for cardiovascular disease such as blood lipids or hypertension." Suggest the inclusion of left ventricular hypertrophy (LVH) and ejection fraction is included as an outcome for the coenzyme Q10 heart failure studies as the literature would not suggest that coenzyme Q10 plays a significant role in reducing stroke or CAD. Your reference 88 (Soja and Mortensen, 1997) cited on page 21 indicates such.	See previous reply.
Description of coenzyme Q10 studies. Do not understand the comment that trials could not be pooled due to heterogeneity in population type when the referenced studies are in patients with heart failure and the data tables (page 93) list the population as "unspecified." Two studies had insufficient follow-up time (less than six months). If a more appropriate outcome measure were used, such as LVH, or ejection fraction, or possibly change in New York Heart Association Class function, three months might be a sufficient time period for study. (Franklin Rosenfeldt, Victoria, Australia has recently performed a meta-analysis on 7 trials that were double blind and placebo-controlled using a three month time point).	See previous reply.
Looking at the Conclusions on p. viii and the Findings on p 4, they only mention vitamin E. Nothing is said about the other two agents of interest (vitamin C and coenzyme Q10), even to say that there were no trials of these agents that could be reviewed. I think an explicit statement about each agent needs to be included in the Summary, and the Conclusions.	See previous reply.
The stated objective of the report included a review of the efficacy of the three antioxidants for the prevention and treatment of cardiovascular disease (CVD) or its risk factors. However, virtually the entire focus of this effort is devoted to three outcomes: death, MI, and/or blood lipid levels. Thus, other research approaches involving human studies (or even cell cultures and animal models) and examining other biomarkers of CVD risk (such as resistance to LDL oxidation, vascular reactivity, No production, hypertension, anti-platelet activity, carotid artery intima-media thickness, smooth muscle cell proliferation, oxidative stress, etc.), although briefly mentioned in some sections of the report, were absent from the equation for evaluating potential benefits and risks.	Within the resources available for this project, we focused on patient outcomes death, MI, and only the intermediate outcomes that were the best evidence supporting a direct relationship with patient outcomes. Other intermediate outcomes were not assessed. We did not assess animal studies or *in vivo* studies.

Elevated blood lipids are an established risk factor for CVD and are thus a reasonable risk factor to consider. However, even a cursory pre-review of the literature would have indicated that antioxidants do not have any significant effect on blood lipids.	These were a commonly reported intermediate outcome and a biological rationale from *in vivo* work, hence we included this in our analysis.
While the selection of the three antioxidants was determined by the contracting Agency for Healthcare Research and Quality, more detail should be provided concerning the large body of evidence indicating a putative beneficial role for the carotenoids and plant polyphenolics (such as the flavonoids). This information would help provide a better context for the question of why antioxidants are an appropriate area of focus for CVD research, especially future research.	Change made to future research.
As the objective of the report concerns antioxidant supplements, particularly in the context of CAM, it is not clear why so much effort was expended in the report detailing the relationship between dietary antioxidant intakes and CVD risk.	This material was included in the Introduction section so that readers could understand the context for the clinical trials.
Regarding safety, in contrast to the statement that: “For vitamin E, few adverse events have been reported in clinical trials for doses up to 1000 IU”, it should be noted that large scale, long-term, randomized clinical trials have employed doses of 2000 IU daily without indication of toxicity (e.g., Parkinson Study Group. *Ann Neurol* 1998;43:318-25 and Sano et al. *N Engl J Med* 1997;336:1216-22).	Change made to the Introduction section.
Discussion of the potential adverse consequence of vitamin C supplementation in enhancing the bioavailability of iron fails to note the absence of data indicating this is actually a speculation unsupported by *in vivo* clinical studies or other reports.	This sentence was deleted.
Little consideration is given to such critical issues as antioxidant dose or form, rationale of antioxidant nutrient combinations, use of intermediary biomarkers of compliance and therapeutic action, and duration of the studies. The differential bioavailability and biopotency of the *RRR* - and all-*rac* forms of *a*-tocopherol are barely considered in the report. It is disturbing to note the report provides obsolete and inaccurate nomenclature for vitamin E (i.e., discussing the D isomers), fails to mention the new RDA redefined vitamin E requirements to be met only by 2*R* forms of *a*-tocopherol, and does not describe the central role of the hepatic *a*-tocopherol transport protein.	These concerns are limitations of the empiric data regarding what makes a study of antioxidants "good quality" and we have noted in the limitations and future research that more attention should be paid to these issues to determine if they are critical to the action of antioxidants in CVD.
Discussion of dose-response relationships concerning coenzyme Q10 is absent although the compelling data from Shults et al. (*Arch Neurol* 2002;59:1541-50) suggests that the null results from clinical trials of coenzyme Q10 in CVD and Parkinson Disease may be due to too low doses.	We did not do pooled analysis of coenzyme Q10 for reasons stated in the text. The Schults article was published after we submitted the report.
Please revise text and tables to consistently refer to each trial by a consistent identifier (trial name) and use reference numbers/author name to identify specific studies associated with each trial.	Change made.

Was vitamin E given with food in the trials as is necessary since it is better absorbed? The GISSI trial was performed in Italy and a benefit was found in a population consuming a relatively fatty breakfast not seen in the US.	This information was generally not stated in the published reports.
This is a very clear and comprehensive analysis and as with the cancer report, I am left with the feeling that your analysis is far more rigorous and well executed than the actual clinical studies being analyzed. The major strength of the report is its comprehensiveness and rigor, while the major limitation lies in the limitations of the clinical studies being analyzed. There are a few studies that use vitamin C alone, and few that include vitamin C in high enough pharmacologic doses to reasonably expect a clinically observable result. The conclusions starting on page 61 and the summary therefore, speak mainly to vitamin E and to vitamin E "in combination".	Only response is to add one sentence in the Limitations regarding vitamin C dose.
The major strengths of this report include question formulation and study identification. The major limitations are study selection and data synthesis.	No response.
However, there was a critical lack of discussion on the dose, formulation and quality of the antioxidant interventions used in the studies that were included in the final analysis.	We have added to the Limitations that a potential explanation for negative studies is that a beneficial dose and formulation of antioxidants has not yet been studied.
Middle paragraph line 4 and elsewhere – you use the words "unique trials". What does unique mean in this context?	Change made in Summary and Methods.
Were the coronary artery disease regression studies not appropriate for inclusion as a separate category? You mentioned the HATS study and another one. Two additional studies have recently been reported which may be beneficial to incorporate – the VEAPS and WAVE studies. Others ongoing are the SECURE, SMARTFED and MCBIT.	We could not find VEAPS study; the WAVE study has now been included.
You state that there is a 20% reduction in all cause mortality in ATBC and Linxian trials. I think this is incorrect. There is a 9% reduction in Linxian; you cite no results from ATBC on all-cause mortality although I don't believe it was reduced (there may not have been a 4 way analysis of these results). You ignore the findings of GISSI on all-cause mortality.	This was a typographical error and has been corrected.
Under all-cause mortality, I think both GISSI and Linxian reported a 20% (not 70%) reduction. And the same for CV death with GISSI (20%, not 70%). The 20% figures are given on p vii, so if that is wrong, it will have to be changed there instead.	See previous reply.
The statements (p. 63) specifying the 70% reduction in risk of all cause mortality and CVD death from the GISSI and Linxian trials is presumably a typographical error.	See previous reply.

There are, however, some errors in the summary statements, the most important of which are on page 63, in which all-cause and cardiovascular mortality are reported as being reduced “70%” in the GISSI trial (it should say 20%).	See previous reply.
Provide one overview table describing the major trials, separated by primary and secondary trials, which summarize the patient population, interventions, follow-up and outcomes reported (combining the various publications from each trial). The trials should be organized by primary and secondary prevention. Within each category they should be organized by interventions and size (or whoever you choose).	Table added that summarizes studies based on primary or secondary categorizations has been included at the beginning of the Results section.
Finally, there are no references attached to large sections of text (the Linxian trial).	Change made and reference added.
On page 36 the ATBC sub-population with coronary disease is described to have been given 400 or 800 IU of vitamin E. I believe they were given the same 2X2 factorial design with 50mg Vitamin E and beta carotene or placebo as the remainder. The description of vitamin E dosing is that in CHAOS (Stevens, Lancet 1996, and page 36).	Change made and reference added.
The purpose of this evidence report is stated to be to identify and assess the evidence for the efficacy of three antioxidants to affect cardiovascular disease or modification of known risk factors. On p 8, cardiovascular disease was defined as a number of conditions, and risk factors were defined as hypertension, hypercholesteremia, smoking and diabetes. Yet for the rest of the report, clinical outcomes of interest were limited to death, cardiovascular mortality and myocardial infarction, and the only risk factor discussed was lipid levels. The reason for limiting to this subset of the original purpose needs to be stated.	For the vitamin E studies, there was a sufficient number of clinically similar studies to justify meta-anlaysis. The three outcomes - death, MI, and lipid levels - were the most commonly reported outcomes in the vitamin E studies, and therefore, they were chosen for the meta-analysis. For vitamin C and coenzyme Q10, we limited our review to studies that reported clinical outcomes or intermediate outcomes with good evidence of a relationship to clinical outcomes. We have added at several points to the text new language to try and make this reasoning clear.
6 lines up from the bottom – 6% deaths from heart failure – seems a very low number. It may be important to quote lifetime risk of developing heart failure (see Lloyd-Jones et al. Circulation 2002;106:3068-72)	The 6% number is accurate. We also added the lifetime risk and Lloyd-Jones citation.
1st paragraph line 4 – 5-9 servings – is this per day, week, year?	Interval should be per day and change has been made to the Introduction.

Selecting another popular antioxidant, such as selenium, would be useful. I am surprised that selenium is repeatedly omitted from these reports. It may be even more important in terms of the antioxidant network and interactions among antioxidants than the examples used in the discussion of antioxidants on pages 14 – 16, for example. Although glutathione is important in the network, it is an endogenous component that may or may not be influenced by supplements. However, selenium clearly interacts with and complements the action of vitamin E, and in turn vitamin C. The evidence for this is quite strong and may be among the most potent interactions in terms of LDL oxidation. Such discussion may be superfluous given that selenium was not selected among the supplements studied, but it is certainly an important antioxidant to consider for future evaluation of the data pertaining to antioxidants and disease prevention.	We cannot add new topics at peer review stage. The topics were set by the sponsor. This is a good suggestion and has been added to future research.
Second paragraph, reference #76 (Aberg, 1998) does not appear to be an article related to statins but to Gemfibrozil – a different class of lipid lowering drugs.	This reference has been deleted.
12 lines down - ? compared with similar patients – without clinical evidence of atheroma.	Change has been made.
Second paragraph under “Safety” first sentence, qualify what you mean by “higher doses of vitamin C”.	Change made.
I am very uncomfortable with the exclusion on p 21 under “Safety of Antioxidant Supplementation” of the observed increase in risk of hemorrhagic stroke with vitamin E seen in the ATBC trial. To omit this at all, but especially after referring to vitamin E’s effects on platelets, seems inappropriate.	Change made.
Qualify what you mean higher doses of coenzyme Q10.	This editing error has been corrected in this revision. Change made.
On p. 36 there is a mention of two different doses of vitamin E in the ATBC trial – I don’t think this is correct.	The reviewer is correct. This typographical error has been corrected.
I could find no description of the Primary Prevention Trial, although I think one sentence describing ceasing trial due to benefits of ASA on p. 37 bottom refers to it.	Description of the Primary Prevention Trial added.
You say PPP and ASAP are secondary prevention – I think you mean primary prevention.	This sentence with this typographical error has been deleted.
First paragraph, sentence beginning “The former trials (PPP and ASAP) are secondary prevention trials” on page 38 you include the PPP and ASAP in the list of four primary prevention trials. Were they both? Which is correct?	This sentence with this typographical error has been deleted.

I disagree with the inclusion and exclusion criteria used to select articles. In fact, I believe selection criteria are applied in a manner that does not limit bias. Specifically, it is unclear to me why studies of lipids and blood pressure are included. Further, it is also unclear why lipids and not blood pressure are selected for further analysis.	Lipids and blood pressure were initially included as acceptable outcomes as they are intermediate outcomes with good evidence of a selection to clinical outcomes. Lipids alone were used in the meta-analysis as they were the most commonly reported intermediate outcome with a biologic rationale for an effect.
The important parameters are systematically addressed but I believe randomized design is under emphasized and other features over emphasized in data synthesis (see below). In the decision to conduct meta-analyses, I believe the key feature is the randomized design. I believe that the decision regarding randomized trials of vitamin E to separate small from large trials is poorly defended, in part, because I believe it is poorly defensible. For coenzyme Q10 also the key is randomization not length of follow-up or use of placebo. Furthermore, ATBC was a randomized, double-blind, placebo-controlled, 2x2 factorial trial of vitamin E and Beta-carotene. The most appropriate comparison is all vitamin E against all vitamin E placebo. In addition, the GISSI trial tested vitamin E and omega-3-fatty acid supplementation in a 2x2 factorial trial. To the best of my knowledge, no other antioxidants were randomized in that trial. Finally, evaluating all vitamin E against all no vitamin E in GISSI yields largely null results.	The stratification of trials of vitamin E based on sample size was done because pooling all together would make the overall pooled results totally based on the one or two very large studies, i.e. the smaller studies would be statistically meaningless. Rather than lose this information, we pooled the smaller studies and compared these results with the large studies. Regarding coenzyme Q10, we agree randomization is important, but disagree with respect to blinding (since this can introduce bias) and duration of treatment or follow-up (since the effects may be transient). We are now more cautious in the conclusions drawn from GISSI.
Many studies were excluded because outcomes of interest were not reported, and it does not appear that there was any effort to contact the study investigators in order to elicit supplemental data. While it seems unlikely that these additional data would materially affect the analyses, the report and its conclusions would be considerably more robust had these data been included.	The resources available precluded us from seeking unpublished data from the original researchers.

There is, however, one aspect of the data synthesis that I find troublesome, and this relates to the analysis and reporting of the vitamin E data from GISSI. GISSI was a prospective RCT utilizing a 2x2 factorial design to evaluate the effects of vitamin E and n-3 PUFA on major cardiovascular outcomes. A total of 11,324 subjects were enrolled, and in the vitamin E allocation, 5666 were assigned to vitamin E and 5668 were assigned to placebo. In the primary paper from GISSI (Lancet 1999;354:447-55), it is stated that there was no interaction between vitamin E and n-3 PUFA; therefore it seems that the fundamental criterion for a 2x2 factorial design was satisfied (i.e., independence of the 2 interventions), and that it is thus most appropriate to analyze the data for the entire population of subjects randomized to vitamin E or placebo. As reported in the GISSI publication, there was no suggestion of a beneficial effect of vitamin E on any major primary or secondary cardiovascular outcome in two-way analysis considering the entire population, a finding wholly consistent with the results of the analyses conducted as part of this Evidence Report. When 4-way analysis was performed, however (i.e. comparing outcomes across the 4 subgroups created by the 2x2 factorial design), there suddenly appeared an apparent beneficial effect of vitamin E on several secondary outcomes. I have difficulty understanding how this could happen, and I am skeptical about the validity of these findings. Therefore, I think that additional discussion of the GISSI data, and its potential limitations, is warranted, so as to avoid giving the impression that this large randomized trial of vitamin E showed improved cardiovascular outcomes, a conclusion that is in fact at odds with how the GISSI group itself interpreted their results.	We have noted in the results and summary that the two way analysis of vitamin E did not show an effect and that the GISSI investigators did not consider their data to prove that vitamin E supplementation is beneficial.
Also, an important limitation of the report is that individual patient data were not available, thus limiting exploratory analyses of relevant subgroups.	The resources are not available for us to seek unpublished data from the original researchers.
Within the confines of the objectives for study identification, no crucial pieces of information were missed. However, isoprostane should not be employed as a search term for coenzyme Q10 (coQ).	This term was included in our search strategy, but no titles or articles were selected based on this term, so this comment is moot.
Search terms. Is isoprostane and appropriate search term for coenzyme Q10? Should ubiquinol (the reduced form as it is present in the blood and on the lipoproteins) and neuquinon be added to the list?	See previous reply.

It appears that the intent to conduct a meta-analysis on the three pre-specified endpoints distracted the authors from extracting other relevant information from most of these studies.	The three outcomes selected for meta-analysis were chosen after examining our list of all outcomes measured in all reports. The three outcomes selected were those that were mose relevant to patients and most commonly reported. So, while we assessed whether other outcomes were reported, our findings indicated the data were too sparse to support a summary analysis either quantitative or qualitative.
I think the meta-analysis is a useful contribution to this literature. However, in isolating individual outcomes from trials, not all of which reported the identical outcomes, one loses the context provided by looking across outcomes for a trial. I also think that information from the 2x2 analyses, which may be inappropriate for meta-analysis, should be retained somehow. I would like the authors to consider how they might incorporate the results of their meta-analysis into a discussion that addresses the more complete data and context more thoroughly. The organization of the text is completely driven by the desire to conduct a meta-analysis of specific endpoints. While that is understandable, it defeats the purpose of conveying any overall sense of the consistency of findings within a trial. For example, the findings in GISSI that CVD mortality was significantly reduced looks a lot less impressive when one sees that there was no effect on overall CVD event rate. Moreover, the significant result on CVD mortality in the 4 way analysis (vit E only vs. placebo only) disappears in the 2 way analysis (comparing all patients who got vitamin E to all those who didn't). Similarly, the trend towards a benefit on non-fatal MI in a subgroup of ATBC with prior CHD is similarly undermined by observing that fatal MIs were increased, and that there was no benefit on total CVD events. The insistence on using only the 4 way results in the 2X2 factorial trials seems to have excluded potentially useful information. Again, it was so hard to follow what was included, when and why that maybe those results got mentioned but I can't be sure. Lastly, one could take issue with the decision not to pool primary and secondary prevention trials for MI outcomes – some trials included in the secondary prevention like HOPE had some patients without prior CHD. And some primary prevention trials had some patients with underlying vascular disease (at least in some analyses).	We have incorporated into this revision more information about both GISSI and ATBC so readers can get a better understanding of these trials. We also have tried to revise the organization to be more clear.
Composition of the Technical Expert Panel. Noted absence of a nutritionist, expert in biochemistry/metabolism and/or cardiovascular medicine.	The TEP for the NCCAM project was consistent from project to project and inevitably did not include all the relevant disciplines. These persons were included at the peer review stage to ensure that their expertise were incorporated into the report.

The searching strategies appeared appropriate. Reference was made to the Technical Expert Panel (p 25) that advised on search and inclusion criteria and appropriate analysis. However, the expertise of the Panel as listed did not include either cardiovascular disease or antioxidants, so their relevance to the design of this report is unclear.	See previous reply.
Extraction of Data, second paragraph. Comment on the equivalence of units for data extraction. I'm very pleased to see this but would like to see it taken a step further to equivalence in terms of supplement formulations, i.e., synthetic vs. natural. I feel very strongly that an attempt to standardize (for statistical analysis) the doses used in these trials should be made, as levels of bioactive ingredients are key. It has been shown that synthetic all rac-alpha-tocopherol increased plasma alpha-tocopherol concentrations only half as much as the natural form of RRR-alpha-tocopherol, and degradation of the synthetic form is 3-4 times that of the natural form (see Brigelius-Flohe, Am. J. Clin. Nutr. 2002;76:703-16 as well as IOM, 2000 DRI report for vitamin C, vitamin E and carotenoids). It would be helpful to incorporate this information in the data analysis tables (Tables 3-17) under the Intervention column.	While available for many trials, this information is not available for all trials. We were also unclear how we might adjust for differences in formulation or potency over time, so while we agree in principle with this comment, we did not think we could do this in our analysis.
First paragraph. I don't believe we know the most clinically relevant dose for the antioxidants, and again, dose and formulation do matter. The dose and formulation used in one study, i.e. HOPE 400 IU of natural alpha-tocopherol, may not equate with 300 mg of synthetic alpha-tocopherol used in the GISSI study. Similar problems exist for coenzyme Q10 formulations as the fat-soluble preparations have higher absorbability, which for CoQ10 is extremely low. CoQ prepared in soybean oil is the preparation regarded as the standard for clinical trials. Doses over 100 mg/day need to be delivered in divided doses, preferably with meals.	Change made: added to Limitations. That knowledge about dose and formulation is inadequate at this point in time.
I believe that the methods of study selection and data synthesis in this report could potentially bias the overall conclusions. In these instances, however, virtually all the data on clinical cardiovascular disease outcomes from individual trials are null (with the possible exception of CHAOS) so the conclusions are not materially affected.	No response.
I have trouble with the quality of the trials being reflected in the "Jadad" score. While this is a formal methodologic definition of quality, I do not see it as directly addressing the issue of quality of the science or scientific design. It does not appear that many, if any, high quality scientific trials have been performed to examine vitamin C in cardiovascular disease. If that is the case, it may be somewhat misleading to say that there is "no evidence" for a beneficial effect when the clinical experiments are biologically so unlikely to provide a positive result.	Perhaps not to examine vitamin C alone in the prevention of cardiovascular disease, but we judge the MRC/BHF study of vitamin C in combination with other agents to be both a high quality study and to report good evidence of no benefit.

The discussion among the scientific community regarding the outcome of AO studies and CVD prevention is that we may have approached the question incorrectly and studied (or compared) the wrong subject groups. Perhaps the draft should incorporate somewhere in its conclusions the idea that when subjects with relatively low antioxidant levels are studied, a stronger treatment effect may be found.	Change made to future research and Limitations.
One of the objectives of this report was to determine if statistical results from various studies could be pooled. This was shown in most instances to be true with some important provisions. As in the case of the SPACE study discussed above, there may be problems with pooling some primary or secondary intervention trials. When the results of studies such as VEAPS, GISSI or SPACE are to be compared, it is clear that the subjects are very different. Pooling such data may be too results confounding and is misleading.	All of the following comments concern the suitability of pooling certain studies. We agree that this is always a source of concern, with no "right" answer. To deal with these concerns, we performed sensitivity analyses, dropping the SPACE Study and the study by Haeger. This did not effect our results. We also note that the event rate in the placebo group in the GISSI and HOPE Study are similar, and this supports our decision to pool these studies.
There are problems with inclusion and exclusion criteria for selected articles that introduce bias for meta-analysis. For example, the SPACE study (Table 3, 5, 6, 8,10) (Boaz, Lancet 2001) specifically addresses vitamin E in patients with coronary disease and end stage renal disease on dialysis. The results should be mentioned as evidence of potential benefit of vitamin E, but not included in tables of secondary prevention or included in pooled analysis.	See previous reply.
The appraisal of studies is an area of concern. The outcome parameters are addressed ignoring clinical status of the subjects that limit the appropriateness of meta-analysis and lumping. For example, in GISSI Provenzione (Lancet, 1999) all 11,000+ patients had a myocardial infarction (MI) within the previous 3 months, in CHAOS patients had angiographic CAD and not necessarily previous MI (page 36), and HOPE did not require coronary disease and included diabetics and hypertensives without known disease. While each is a “secondary prevention” trial, I don’t think they can be lumped without inducing a possible dilution bias. I appreciate the Evidence Report Study Group would have considerable difficulty with these differing entry criteria and thus the weakness of meta-analysis.	See previous reply.

Data synthesis is the area I am most concerned about. There is lumping of studies for primary and secondary prevention that introduces bias. For example, the SPACE study by Boaz, Lancet 2000 (Table 3) evaluates vitamin E in a population with end-stage renal disease on dialysis. The effects of dialysis on CV outcome are so important this study should not have been included, albeit it did not influence outcomes. Similarly, the study by Haeger in 1968 (Table 3) using vitamin E in peripheral vascular disease was conducted in a time in which therapy and diagnosis was so limited I would not include it.	See previous reply.
The report indicates that evidence of benefit was not obtained in the pooled analysis of smaller trials of vitamin E (alone or in combination) and contrasts this null outcome with the reduction in mortality found in the ATBC and Linxian trials. The repeated comparative reference to these results suggests a less than adequate appreciation of the difference between the secondary prevention intent of the smaller trials and the primary prevention objective of the larger trials.	We revised our text to be more guarded in our conclusions regarding the mortality differences seen in ATBC and Linxian. Normally we would expect a secondary prevention trial to be more likely to show an effect than a primary prevention trial, all other things besides patient risk being equal (which is the opposite seen here). The "difference" in the results in this collection of studies may be more a consequence of the ability to test multiple subgroups in the larger trials.
Little mention or consideration is given to the increase in fatal MI observed in the CHAOS trial or the increase in hemorrhagic stroke found in the ATBC. While these results may be explained as spurious or described as unconfirmed by other studies, these data must be provided appropriate emphasis in this report.	Change made in the Safety section of Introduction for ATBC and the increase in fatal MI in the CHAOS study is already indicated in Table 12 and Figure 12.
I don't think there was any bias, but the clinical differences between studies are so great I don't believe a meta-analysis or lumping is appropriate. From my perspective I could see lumping the results of the British Primary Prevention Program and BMC/Heart Protection Study. While HOPE and GISSI were both secondary prevention studies, the HOPE study would dilute the GISSI results because patients were lower risk.	Our calculation shows that the event rates in the HOPE study were comparable to the rates in GISSI trial, supporting a decision to pool.
Meta-analysis of Vitamin E Alone vs. Placebo: first paragraph, second sentence notes that "a fifth smaller trial is also included in this meta-analysis" however this trial is not identified by name or author in the text (but is referenced). This study was performed in 1968, were comparable design methods and antioxidant formulations utilized?	Change made and results redone dropping this study as a sensitivity analysis.
You include the vit E + PUFA results under the table vitamin E + other vitamins. PUFA is not a vitamin, however, and if it has any benefit it is probably not as an antioxidant but through effects on thrombogenesis.	Correct, we changed the names of this category to "vitamin E in combination".

In the first paragraph on p 35, the MASIT trial was referred to, but there was no description of the trial in the next section on “Details of Named Trials”.	Change made.
The Linxian Nutrition Intervention Trial (page 36) was conducted in a population of Chinese who were known to be vitamin deficient to determine the value of micronutrients on esophageal cancer. As stated the CVD outcomes were not the primary goal of the study. The baseline clinical examinations and measures of CVD at outcome are not at the same standards of the other studies.	This limitation of the Linxian study was added to the Limitations section.
Details of the “Named” Clinical Trials… In the text description, if the details regarding formulation are not added to the data tables, then you may want to provide the specific formulation of the interventional agent (natural, synthetic, lipid soluble, etc) in the text.	Change made. Descriptions added.
There is an error on page 37, last sentence regarding the MRC/BHF study: ASA should have been simvastatin.	Editing mistake has been fixed.
Benefits of ASA? – is this aspirin?	See previous reply.
Trial Inclusion. Perhaps some explanation on the rationale for six months as the minimal appropriate time for adequate assessment. If this were a statin trial, would six months be a minimal appropriate time for adequate assessment for an outcome of MI? Most statin regression trials run for at least two years. Why would we expect vitamin E to be more powerful than a statin in preventing MI?	As it turned out, mostly all of the studies had two years duration of treatment, so this comment is moot.
The description of the different ATBC analyses is confusing. The text on p. 46 implies you used the primary prevention analysis in the pooled analysis but I don’t think that is true but there aren’t references attached with specific statements in the text.	Change made.
Third paragraph, first sentence. Please identify “an additional trial” and its text by name or author and its respective risk ratio as well as providing the reference citation.	Change made.
You state the largest study was the ATBC – that is not true for the subanalysis you rely on. The table and forest plot on non-fatal MI make it clear that the two largest studies showed no benefit on non-fatal MI. Only a subgroup analysis of ATBC suggests a benefit, along with some other small studies.	The reviewer is correct. We changed the text to reflect this.
It is not clear why the ATBC results for primary prevention portion are not included in tables but are described in text. My understanding is that one of the analyses eliminated those with prior CVD, so you could avoid overlap. Even if not, it is worth including in table (not meta-analysis) with footnote if there is an issue of overlap.	Change made to the "not-pooled" section of relevant tables.

Second paragraph, seventh sentence describing the other study (not identified in text by name), which is a study in patients following PTCA. Is this patient population considered comparable to those in the other secondary prevention trials as PTCA increases vascular reactivity and can enhance the disease process?	While the patient population was at high risk, we did not consider this study further because of follow-up time. 3-28 days was not comparable to the other studies.
Summary – I think this section is inaccurate. You state that the benefits of ATBC suggest a benefit for vitamin E alone for fatal MI, when it is GISSI (according to your tables) not ATBC suggesting benefits against fatal MI. For non fatal MIS, both CHAOS and ATBC subgroups suggest possible benefit, but you state on page 50 that the ATBC results for the general population suggest a benefit on nonfatal MIs. There was a trend toward benefit only in a subgroup with prior MI, but no benefit in the larger population of ATBC participants.	Corrected in text. Factual errors were corrected in the results section.
Last line paragraph 2 – "heterogeneous sample size" – meaning?	Large differences between trials in sample size text. Revised to make this clear.
First paragraph. Last sentence – "attempts to stratify the analysis by vitamin E dose level were not helpful." This is important, could the same be done for formulation: synthetic vs. natural at high and low doses? Same comment for analysis of HDLs and meta-analysis parameters.	The data are insufficient to support this analysis.
Second sentence is unclear as written. "A small negative effect not favor of treatment was shown."	This sentence was revised.
The decision to pool clearly heterogeneous results seems problematic, especially without some attempt to explore reasons for the heterogeneity. The two largest studies show no benefit, but the pooled result is driven by small, outlier studies. The text could do a better job of explaining this result as it may be misinterpreted.	We revised the text to try and better explain this.
The tables in Table 6 and 7 cite the identical number of deaths for GISSI results under vitamin E alone and Vitamin E + other vitamins. This is presumably an error. My suggestion is to delete the vitamin E + PUFA results altogether but if you keep them (there may be a case for doing so I don't know this area intimately) you need the correct figures for that arm.	These numbers have been double-checked for accuracy.
The report's overall conclusion is that the three antioxidants alone or in combination do not have a significant effect on the treatment and prevention of CVD. However, these conclusions cannot be made categorically as evidence from some studies suggest that some protection is conferred and in some instances AO use can confound or even worsen the effects of other interventions. It is important to emphasize that further studies are needed, especially using specific populations, to better understand the effects of AO supplements. This is clearly indicated in this draft and I find it to be among the most important conclusions or recommendations of this report.	No response.

There is insufficient comment about the potential positive outcomes from intermediate trials or studies that were complicated by multiple interventions or other complexities. This is especially true for studies that used subjects with disease that predispose to cardiovascular disease (e.g. SPACE trial).	This limitation was added to the Limitations and Conclusion sections.
Drawing conclusions on the potential role of antioxidants in CVD prevention and treatment, as noted above, by using only death, MI, and/or blood lipid levels as evaluative criteria likely underestimates their true value by ignoring their impact on other relevant parameters such as antiplatelet actions, vascular reactivity, antihypertensive capacity, and impact on the risk for related diseases like diabetes.	The intermediate outcomes listed by this reviewer were not assessed in this report because their relation to clinical outcomes (death, MI) are not firmly established. Within the resources available to us, we concentrated on clinical outcomes and intermediate outcomes with strong evidence of an association with clinical outcomes. Whether lack of assessment of these other intermediate outcomes underestimates or overestimates the effect of antioxidants on patient outcomes is unknown.
I agree with your conclusions but am doubtful surrogate endpoints will be of any value. They encourage extrapolation to the positive and don't address risk adequately. Physicians Health Study 2 will address long term use of vitamins. I favor targeting well-defined high risk populations such as diabetics with CAD, a high risk group that can be studied over a relatively short period.	Added to future research.
The major issue with antioxidants is that studies were stopped early because of outcome of other arms such as omega 3 fatty acids in GISSI, ramipril in HOPE, and simvastatin in BMC/HPS. There is a reasonable possibility that the benefit of antioxidants won't be reached for 10 years. Hopefully, the Woman's Health Initiative that is looking at vitamins will continue that arm regardless of other results.	Change made in Limitations.
The other issue is the potential for pro-oxidant effects of vitamin E and the need for combining vitamin E with a tissue antioxidant such as coenzyme Q-10.	This was added to future research.
Also, on page 62, line 5, seven outcomes are listed (not eight), and on page 64, line 14, it appears that the authors mean "fatal myocardial infarction" (not "all cause mortality").	Change made.
Similarly, on page 67, line 19, "total cholesterol" is incorrect; it should read "HDL cholesterol".	Change made.
I also disagree that further research on antioxidants is needed with surrogate endpoint. Finally, as regards coenzyme Q10 depletion does not imply that supplementation will lead to clinical benefit. For these reasons, rather than simply state further research is needed, I would emphasize that randomized trials, not observational studies are needed to avoid previous pitfalls with other antioxidants.	Agreed

First, since the population of RCTs is overwhelmingly comprised of middle-aged white males, there is a need for studies evaluating the effects of antioxidants in the elderly, women, and racial/ethnic minority groups (esp. blacks and Hispanics).	Added to future research.
Second, although this report focuses on mortality and major cardiovascular events, other endpoints may be relevant in selected patient populations; e.g. it is conceivable that coenzyme Q10 improves symptoms in patients with heart failure but does not reduce mortality, or that vitamin E has a favorable effect on preserving cognitive function in the elderly (as suggested by one study) without affecting mortality or cardiovascular events.	Agreed, although for the purposes of their report a presentation of cognitive function would fall outside our scope.
While it is evident that research focused on understanding the conflict between the largely consistent and compelling CVD primary prevention data with supplements and the largely null and discouraging CVD secondary prevention results with supplements, this "paradox" does not include the "beneficial effects of fruit and vegetable consumption". Contrary to the statement in the report that "It was postulated that the antioxidant component of fruits and vegetables accounted for the observed protection" (my emphasis), antioxidants have always been considered only as contributing factors in this context, along with other associated nutritional relationships associated with this dietary pattern (e.g., B vitamins, fat, and fiber).	Changes made to reflect this.
Further research is proposed to test "formulas which showed benefit in larger trials", however, none of these trials (as chosen for this report with its selected evaluation endpoints) provided sufficient evidence or magnitude of benefit to justify such an investment in new research. Similarly, trial interventions employing food concentrates fails to provide any guidance or priority, e.g.: what foods? what ingredients? concentrated how? administered for how long and to whom?	We have resolved this section of future research.
The recommendation to determine if fruit consumption is associated with other behaviors which cause benefit for which fruit consumption is a marker is reasonable. However, it is not clear why a similar recommendation is not proffered for vegetable consumption.	Vegetables have been added.
The recommendation to repeat the interventions which did show positive results is confusing as these studies (e.g., CHAOS and SPACE) have already essentially been replicated (e.g., HOPE and HPS) and shown a null outcome.	Agreed. Change made to future research.
No suggestions for future research are offered which prioritize single antioxidants or combinations for study.	We think this is best left to an expert panel assembled by the sponsor and considering the results in this report.

Similarly, although the need for “appropriate surrogate endpoints or intermediate outcomes” for CVD is emphasized, no suggestions are offered as to which ones might prove most likely to be successful, e.g., biochemical markers, lesion indices, physiological responsiveness, etc.	See previous reply.
Importantly, it should be noted that none of the large clinical trials have employed relevant biomarkers either to validate them or to test the efficacy of the intervention (e.g., increasing antioxidant defenses or lowering oxidative stress).	Added to future research.
Suggestions for future research should include recommendations as well for: [i] documenting full dose-response relationships of the selected antioxidants (N.B.: doses of 1200 IU vitamin E appear required to affect biomarkers of oxidative stress and inflammation relevant to atherogenesis [Devaraj & Jialal. *Free Radic Biol Med*. 2000;29:790-2]), [ii] determining polymorphisms relevant to CVD pathogenesis (including endothelial nitric oxide synthase, 12/15-lipoxygenase, and macrophage scavenger receptors) as well as to redox states, and oxidative stress status (and employing them as inclusion/exclusion criteria), [iii] employing lower risk groups (presumably whom utilize fewer concomitant drug therapies), [iv] exploring the relationship between antioxidant and B vitamin status (as homocysteine is a pro-oxidant), [v] the potential for adverse interactions with pharmacotherapy (e.g., see Cheung et al. *Arterioscler Thromb Vasc Biol*. 2001;21:1320-6).	Most of these have been added to future research.
I believe the statement to be unwarranted that further research is necessary to explain the apparent paradox between results of observational studies and randomized trials. In fact, it should be stated clearly in this report that for many, if not most, expose and disease hypothese randomized trials are neither necessary nor desirable. When searching for small to moderate effects, however, (20-50%) the amount of uncontrolled and uncontrollable confounding inherent in observational studies is as big as the most plausible benefits or harm. In such circumstances, reliable data can only derive from randomized trials of sufficient size, dose, and duration. In my view, observational studies have been misleading for vitamin E, beta-carotene, and postmenopausal hormones.	Agreed. The Future Research section focuses on RCTs.
Perhaps one of the most critical research needs is to identify and standardize the test agent and administer it under the most appropriate conditions.	Agreed. This is included in future research.

The future research sections beginning on page 5 and page 71 might benefit from some revisions. The meaning of the following sentence at the end of "Future Research" on page 5 escapes my understanding; "the observation that higher levels of vitamin C were associated with lower death rate has not been confirmed yet in clinical studies. The explanation of this apparent paradox requires additional investigation as well". By higher levels, I presume you are referring to the serum concentration of vitamin C. If so when one says "higher levels", what is being referred to, higher than what? Likewise, I do not see the apparent paradox. What serum concentration of vitamin C do you think would be associated with a lower death rate?	This section has been revised.
In the Future Research section on p 5, it is stated that a possible avenue of future research would include testing of formulas which showed benefit in larger trials. There was no discussion of formulas in the report, nor any information on what formulation of agent was used by what trial. It sounds like you are suggesting that, for example, trials with promising results all used synthetic vitamin E not natural source (or vice versa). Is this true?	This has been clarified.
It is also stated on p 5 that additional research is needed for vitamin C on risk factor modification and lower death rate, and for co-Q10 on heart failure and cardiac surgery. It felt like these recommendations were coming out of the blue, since there were no statements in the preceding body of the Summary that even mentioned C or coenzyme Q10, and no full discussion in the actual report of an assessment of the status of the evidence of these agents.	This revision now includes data about vitamin C and coenzyme Q10.
It was also stated that surrogate or intermediate outcomes could be useful to do trials more quickly – trials of what? For vitamin E, for example, I can't see any place to go with another trial in CVD.	We have eliminated the suggestion to assess intermediate endpoints.
On page 71 I do not see the scientific logic of the suggestion of using supplements such as food concentrates with respect to vitamin C. Why would taking ascorbic acid in a food concentrate be more beneficial than ascorbic acid? I strongly favor the suggestion to perform studies to ascertain if favorable dietary compositions are markers for other beneficial behaviors. Again on page 71, is the issue of "higher levels" of vitamin C and decreased risk of death would benefit from restatement. I don't see the nature of the apparent paradox, nor is there any specificity of how this should be tested. Should one give very large pharmacologic doses of vitamin C and measure cellular and tissue accumulation?	This recommendation has been deleted.
Bullet 1 it is said to consider interventions which are intermediate between foods and isolated chemical supplements such as food concentrates, etc. I was just unclear what that meant – could you add an example of what that means for vitamin E and C, for example.	This recommendation has been deleted.

The third bullet says to perform careful "cohort trials to determine if fruit consumption is associated with other behaviors . . ." First, it is cohort studies, not trials, and second, did you mean vegetable consumption? – or fruit and vegetable consumption?	This recommendation has been deleted.
In bullet 4, it is stated that in observational studies, vitamin C is associated with decreased risk of death, but that this result "has not been reported in the clinical trials literature using supplemental vitamin C. Further trials could investigate this apparent paradox as well". A "paradox" implies that trials of vitamin C supplements were conducted and did not show a benefit on death. From your report, it appears there were no trials of vitamin C supplementation, which means they have to be done, not that there is a paradox. This needs to be clarified.	This text has been revised.
Bullet 5 says that the interventions that did show positive results need to be repeated to see if they can be replicated – I think it has to be added "to see if the findings were real or due to chance".	Agreed.
Top of p 72 says the most effective formulations for some antioxidants, e.g. vitamin E, have not been clearly determined. Again, this was not discussed in the report in terms of linking results to formulations in completed trials.	This has been deleted.
Comment: Since there are a number of ongoing primary (PHS II, WHS, SU.VI.MAX) and secondary (HPS, WACS) studies, as well as regression studies evaluating antioxidant use and CVD outcomes how should the research recommendations be prioritized or qualified so as to avoid duplication of effort or inappropriate or premature recommendations for future research? Should all future studies be required to utilize the same formulation of test preparation (antioxidant)?	Change made to future research.