Meta-Analysis of the Association Between Whole Grain Intake and Coronary Heart Disease Risk

Gang Tang, MD, Duan Wang, BS, Jun Long, BS, Fan Yang, BS, and Liangyi Si, PhD*

Epidemiologic studies evaluating the association of whole-grain intake with risk for coronary heart disease (CHD) have produced inconsistent results. The aim of this meta-analysis was to summarize the evidence from observed studies regarding the association between whole-grain intake and risk for CHD. Pertinent studies were identified by searching the Web of Knowledge and PubMed up to July 2014. A random-effects model was used to combine the results. Publication bias was estimated using Begg's funnel plot and Egger's regression asymmetry test. Ultimately, fourteen reports of 18 studies (15 cohort studies and 3 case-control studies) involving 14,427 patients with CHD and 400,492 participants were used in this meta-analysis. Pooled results suggested that highest whole-grain intake amount compared with the lowest amount was significantly associated with reduced risk for CHD (summary relative risk 0.787, 95% confidence interval 0.743 to 0.833), with no between-study heterogeneity observed (I^2 = 0%, p = 0.537). The association was significant in cohort studies but not in case-control studies. Inverse associations were also found in the United States and Europe. No publication bias was found. In conclusion, this meta-analysis indicates that higher whole-grain intake has a protective effect against CHD. **(Am J Cardiol 2015;115:625−629)**

Coronary heart disease (CHD) is the leading cause of death in industrialized countries,[1] accounting for up to 40% of all lethal events,[2] and it is expected to be the leading cause of disease burden worldwide by 2020.[3] Health behaviors, including nutrition, should be taken into account to reduce the risk for CHD, according to the American Heart Association.[4] Whole grains include dark bread, whole-grain breakfast cereal, popcorn, cooked oatmeal, wheat germ, brown rice, bran, and other grains. Whole-grain foods contain fiber, vitamins, minerals, phenolic compounds, phytoestrogens, and other unmeasured constituents,[5] which may have favorable effects on health by lowering serum lipids and blood pressure, improving glucose and insulin metabolism, improving endothelial function, and alleviating oxidative stress and inflammation. To date, a number of epidemiologic studies have been published that explored the relation between whole-grain intake and CHD. However, the results are not consistent. Therefore, we conducted a meta-analysis to (1) assess CHD risk for the highest versus lowest amount of whole-grain intake and (2) assess heterogeneity among studies and publication bias.

Methods

We performed a search of published research up to July 2014 using the databases of PubMed and the Web of Knowledge. The following search string was used: "[cardiovascular disease (CVD) OR myocardial infarction (MI) OR coronary heart disease (CHD) OR ischemic heart disease (IHD)] AND (whole grain OR diet OR lifestyle)." Results were restricted to studies conducted in humans. Moreover, we reviewed the reference lists from retrieved reports to search for further relevant studies.

Two investigators independently reviewed all identified studies, and studies were included if they met the following criteria: (1) a case-control or prospective design was used; (2) the exposure of interest was whole grains; (3) the outcome of interest was CHD, myocardial infarction, CVD, or ischemic heart disease; and (4) relative risk (RR) with 95% confidence intervals (CIs) was provided. If data were duplicated in >1 study, we included the study with the largest number of cases.

The following data were extracted from each study by 2 investigators: first author's last name, year of publication, study design, geographic locations, sample source, the age range of study participants, the duration of follow-up, and the numbers of cases and participants. From each study, we extracted the RR that reflected the greatest degree of control for potential confounders. If there was disagreement between the 2 investigators about the eligibility of data, it was resolved by consensus with a third reviewer.

The pooled measure was calculated as the inverse variance−weighted mean of the logarithm of the RR with its 95% CI to assess the strength of association between whole-grain intake and the risk for CHD. A random-effects model was used to combine study-specific RRs (95% CIs), which considers within- and between-study variation.[6] The I^2 statistic was used to assess heterogeneity, and I^2 values of 0%, 25%, 50%, and 75% represent no, low, moderate, and high heterogeneity,[7] respectively. Publication bias was

Department of Geriatrics, Southwest Hospital, Third Military Medical University, Chongqing, China. Manuscript received August 27, 2014; revised manuscript received and accepted December 5, 2014.

See page 628 for disclosure information.

*Corresponding author: Tel/fax: +86-13708333627.

E-mail address: siliangyi@yeah.net (L. Si).

0002-9149/15/$ - see front matter
http://dx.doi.org/10.1016/j.amjcard.2014.12.015

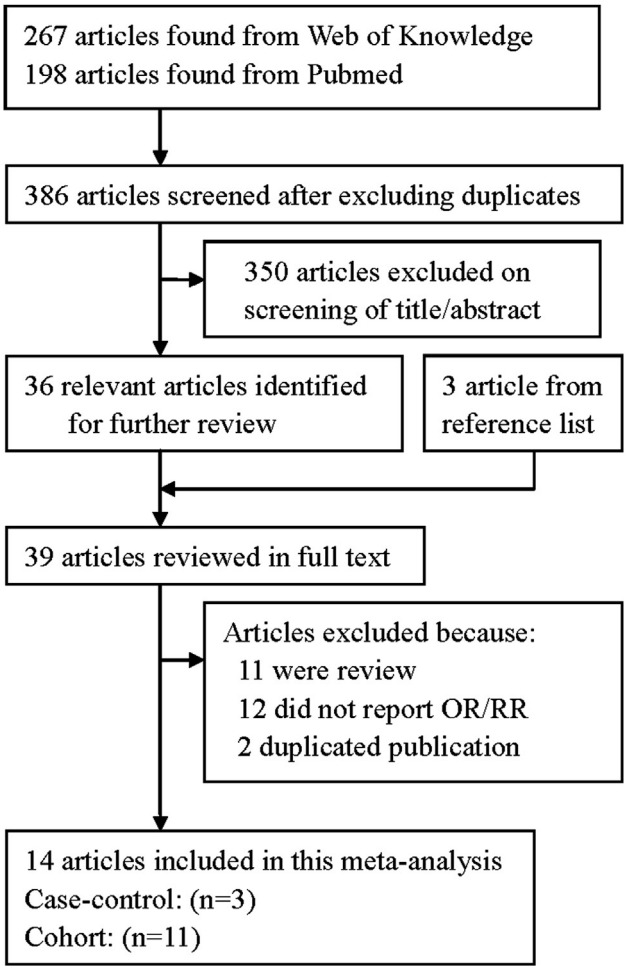

Figure 1. Flow diagram of screened, excluded, and analyzed publications.

evaluated using Begg's funnel plot[8] and Egger's regression asymmetry test.[9] A study of influence analysis[10] was conducted to describe how robust the pooled estimator was to the removal of individual studies. All statistical analyses were conducted with Stata version 11.0 (StataCorp LP, College Station, Texas). Two-tailed p values ≤ 0.05 were accepted as statistically significant.

Results

The detailed steps of our search are shown in Figure 1. Fourteen reports[11–24] of 18 studies (15 cohort studies and 3 case-control studies) involving 14,427 patients with CHD and 400,492 participants were used in this meta-analysis. Thirteen studies assessed whole-grain intake with a food-frequency questionnaire, and 5 studies assessed whole-grain intake with a semiquantitative food-frequency questionnaire. Twelve studies were conducted in the United States, 3 in Norway, 1 in Portugal, 1 in Sweden, and 1 in Italy. The characteristics of these studies are listed in Table 1.

Inverse associations of whole-grain intake and the risk for CHD were reported in 11 studies, and no significant association was reported in 7 studies. Pooled results suggested that the highest whole-grain intake amount compared with the lowest amount was significantly associated with reduced risk for CHD (summary RR 0.787, 95% CI 0.743 to 0.833), with no between-study heterogeneity observed ($I^2 = 0\%$, $p = 0.537$) (Figure 2).

In subgroup analyses for study design, the pooled RRs of CHD for the highest category of whole-grain intake compared with the lowest category were 0.779 (95% CI 0.733 to 0.828) and 0.946 (95% CI 0.605 to 1.478) for cohort studies and case-control studies, respectively. When we conducted the subgroup analysis by geographic location, significant associations were found between whole-grain intake and CHD in the United States and Europe. In subgroup analyses for disease outcome, inverse associations of whole-grain intake and risk for CHD were found for CHD (summary RR 0.782, 95% CI 0.712 to 0.859) and CVD (summary RR 0.762, 95% CI 0.693 to 0.838), but not for myocardial infarction. When we conducted the subgroup analysis by follow-up duration (<10 and ≥ 10 years) and gender, the results was consistent with the overall data. The details results are summarized in Table 2.

Influence analysis showed that no individual study had excessive influence on the association of whole-grain intake and CHD risk. Begg's funnel plot and Egger's test ($p = 0.633$) showed no evidence of significant publication bias between whole-grain intake and CHD risk.

Discussion

Findings from this meta-analysis indicated that the highest whole-grain intake amount compared with the lowest amount was significantly associated with reduced risk for CHD. The association was significant in cohort studies but not in the case-control studies. Inverse associations were also found in the United States and Europe.

Between-study heterogeneity is common in meta-analyses. However, no evidence of between-study heterogeneity was found in the pooled results. He et al[11] and Liu et al[17] used the same cohort from the Nurses' Health Study. Three studies by Jacobs et al[12,13,15] used the same cohort from the Iowa Women's Health Study. This might be the reason for the low between-study heterogeneity. Although they used the same cohort, the studies were different. He et al[11] reported results for CVD, and Liu et al[17] reported results for CHD. The length of follow-up was also different between those 2 studies. Jacobs et al[12,13] reported different case outcomes in 1998 and 1999 from the Iowa Women's Health Study. In their 2007 study,[15] the length of follow-up was 17 years. This was different from the study in 1999.[12]

Several potential mechanisms for the observed association have been proposed. Whole-grain foods contain fiber, vitamins, minerals, phenolic compounds, phytoestrogens, and other phytochemicals that are removed during the refining process.[25–27] Interestingly, many of these compounds can support the antioxidant defense and thereby reduce the damaging effects of chronic inflammation via several mechanisms, including cell-cycle control, protein chaperoning and repair, deoxyribonucleic acid and chromatin stabilization and repair, removal of reactive

Table 1
Characteristics of included studies on whole grain and coronary heart disease risk

Study, year	Study design	Country, Study cohort	Disease outcome	Participants (cases)	Follow-up (years)	Age (years)	Category	RR (95%CI) for highest versus lowest category
He et al. 2010	Cohort	United States Nurses' Health Study	CVD	7822 (295)	26	30-55	32.6 g/d vs. 4.8g/d	0.70(0.46-1.06)
Jacobs et al. 1999	Cohort	United States Iowa Women's Health Study	CVD, CHD	38740 (1779)	9	55-69	22.5 ser/week vs. 1.5 ser/week	0.82(0.66-1.01) for CVD 0.82(0.63-1.06) for CHD
Jacobs et al. 1998	Cohort	United States Iowa Women's Health Study	IHD	34492 (438)	9	55-69	22.5 ser/week vs. 1.5 ser/week	0.70(0.50-0.98)
Jacobs et al. 2001	Cohort	Norwegian Norwegian County Study	CVD, CHD	33848 (1311)	11	35-56	2.25 -5.40 vs. 0.05 - 0.60	0.77(0.60-0.98) for CVD 0.76(0.56-1.02) for CHD
Jacobs et al. 2007	Cohort	United States Iowa Women's Health Study	CVD, CHD	27312 (2934)	17	55-69	≥19 ser/week vs. 0-3.5 ser/week	0.73(0.62-0.86) for CVD 0.72(0.57-0.90) for CHD
Jensen et al. 2004	Cohort	United States Health Professionals Follow-Up Study	CHD	42850 (1818)	14	40-75	42.4 g/d vs. 3.5g/d	0.87(0.70-0.96)
Liu et al. 1999	Cohort	United States Nurses' Health Study	CHD	75521 (761)	10	38-63	2.7 ser/d vs. 0.13 ser/d	0.79(0.62-1.01)
Liu et al. 2003	Cohort	United States Physicians' Health Study	CVD, MI	86190 (1869)	5.5	40-84	≥1 ser/d vs. Rarely	0.80(0.66-0.97) for CVD 0.71(0.51-0.98) for MI
Lockheart et al. 2007	Case-control	Norwegian —	MI	211 (106)	–	45-75	240 g/d vs. 94 g/d	0.89(0.35-2.26)
Oliveira et al. 2010	Case-control	Portugal —	MI	3016 (820)	–	≥18	≥ 6 g/d vs. < 6 g/d	0.74(0.62-0.90)
Rautiainen et al. 2012	Cohort	Sweden Swedish Mammography Cohort	MI	32561 (1114)	10	49-83	≥4.7 ser/d vs. ≤2.3 ser/d	0.89(0.74-1.07)
Sahyoun et al. 2006	Cohort	United States Community-living persons	CVD	535 (89)	10	60-98	2.9 ser/d vs. 0.31 ser/d	0.48(0.25-0.96)
Steffen et al. 2003	Cohort	United States Atherosclerosis Risk in Communities Study	CHD	15792 (535)	11	45-64	3 ser/d vs. 0.1 ser/d	0.72(0.53-0.97)
Tavani et al. 2004	Case-control	Italy —	MI	1602 (558)	–	18-79	>2 ser/week vs. <2 ser/week	1.3(0.9-1.8)

BMI = body mass index; CHD = coronary heart disease; CI = confidence interval; CVD = cardiovascular disease; d = day; IHD = ischemic heart disease; MI = myocardial infarction; RR = relative risk; ser = serving.

molecular species, and induction of antioxidant defense and detoxification mechanisms.[27] Many of these compounds are redox-active secondary plant metabolites[26–29] that are produced by plants in response to oxidative and other types of stress and activate defense-related genes in plant cells. It has been suggested that these molecules also can mount an antioxidant defense in animal cells (after intake by the animal) by inducing gene expression of similar genes for antioxidant and detoxification enzymes.[27,30] Therefore, we think it is plausible that whole-grain intake may reduce the risk for CHD.

To our knowledge, this is the first comprehensive meta-analysis conducted to assess the association between whole-grain intake and CHD risk. For the results of analysis, we found a protective effect for CHD with higher whole-grain intake. Second, a major strength of this study was the large number of participants included in this meta-analysis, allowing a much greater possibility of reaching reasonable conclusions and conducting subgroup analysis. Third, no evidence of between-study heterogeneity and no publication bias were found, indicating that our results are stable. However, there were some limitations in this meta-analysis. First, a meta-analysis of observational studies is susceptible to potential bias inherent in the original studies, especially for case-control studies. An overstated association may be expected from the case-control studies because of recall or selection bias, and early symptoms in patients may have resulted in changes in dietary habits. In our meta-analysis, a significant association was found only in cohort studies, not in the case-control studies, while only 3 studies included used case-control designs. Second, although we extracted the RRs that reflected the greatest degree of control for potential confounders, the extent to which they were adjusted and the possibility that the observed association was due to unmeasured or residual confounding should be considered. Third, all studies included were from the United States and Europe, and we found significant associations between whole-grain intake and CHD in both geographic regions. Therefore, the results are applicable to the United States and Europe but cannot be extended to populations elsewhere. More studies originating in other countries are

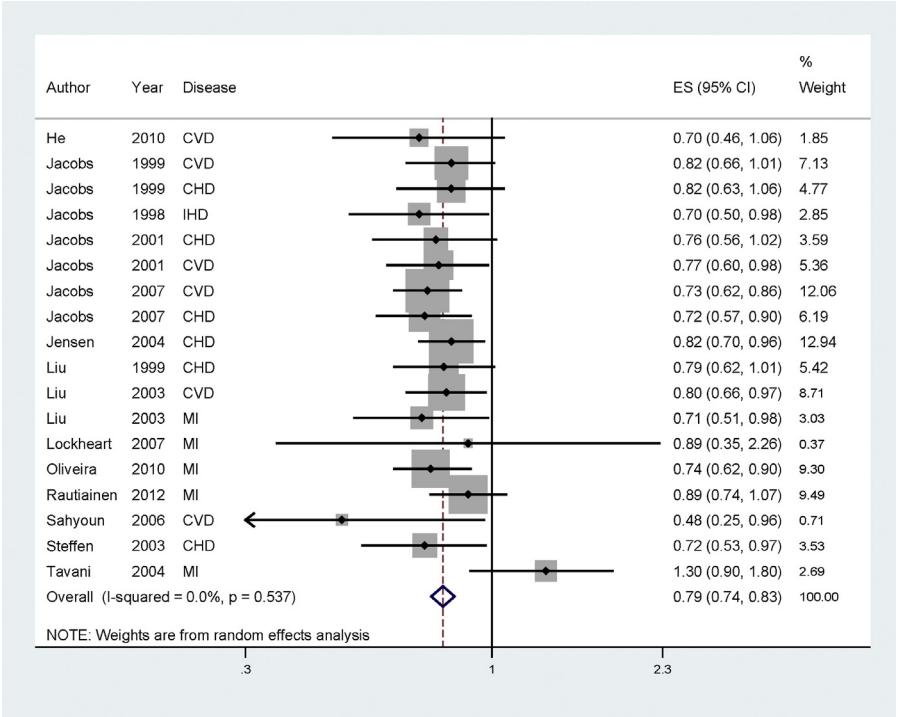

Figure 2. Forest plot between highest and lowest amounts of whole-grain intake and CHD risk.

Table 2
Summary risk estimates of the association between whole grain intake and coronary heart disease risk

Subgroups	No. (cases)	No. studies	RR (95% CI)	Heterogeneity test	
				I^2 (%)	P-value
All studies	14427	18	0.787(0.743-0.833)	0.0	0.537
Study design					
Cohort	12943	15	0.779(0.733-0.828)	0.0	0.928
Case-control	1484	3	0.946(0.605-1.478)	74.7	0.019
Geographic locations					
America	10518	12	0.767(0.716-0.821)	0.0	0.935
Europe	3909	6	0.847(0.728-0.985)	45.4	0.103
CHD outcome					
CHD	5383	6	0.782(0.712-0.859)	0.0	0.934
CVD	5520	6	0.762(0.693-0.838)	0.0	0.708
MI	3086	5	0.864(0.709-1.054)	56.9	0.054
Follow-up duration					
<10	4086	5	0.787(0.704-0.878)	0.0	0.892
≥10	8857	10	0.776(0.722-0.834)	0.0	0.739
Sex					
Females	7879	9	0.807(0.730-0.891)	33.0	0.154
Males	3687	3	0.799(0.712-0.895)	0.0	0.739

CHD = coronary heart disease; CI = confidence interval; CVD = cardiovascular disease; MI = myocardial infarction; RR = relative risk.

required to investigate the association between whole-grain intake and CHD risk.

Disclosures

The authors have no conflicts of interest to disclose.

1. Chen L, Wang X, Bao J, Geng C, Xia Y, Wang J. Direct comparison of cardiovascular magnetic resonance and single-photon emission computed tomography for detection of coronary artery disease: a meta-analysis. *PLoS One* 2014;9:e88402.
2. Franchini M, Peyvandi F, Mannucci PM. The genetic basis of coronary artery disease: from candidate genes to whole genome analysis. *Trends Cardiovasc Med* 2008;18:157−162.
3. Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. *Lancet* 1997;349:1498−1504.
4. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, Bravata DM, Dai S, Ford ES, Fox CS, Franco S, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Huffman MD, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Magid D, Marcus GM, Marelli A, Matchar DB, McGuire DK, Mohler ER, Moy CS, Mussolino ME, Nichol G, Paynter NP, Schreiner PJ, Sorlie PD, Stein J, Turan TN, Virani SS, Wong ND, Woo D, Turner MB; American Heart Association Statistics C, Stroke Statistics S. Heart disease and stroke statistics—2013 update: a report from the American Heart Association. *Circulation* 2013;127:e6−e245.
5. Anderson JW, Hanna TJ. Whole grains and protection against coronary heart disease: what are the active components and mechanisms? *Am J Clin Nutr* 1999;70:307−308.
6. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177−188.
7. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557−560.
8. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994;50:1088−1101.
9. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629−634.
10. Tobias A. Assessing the influence of a single study in the meta-analysis estimate. *Stata Tech Bull* 1999;47:15−17.
11. He M, van Dam RM, Rimm E, Hu FB, Qi L. Whole-grain, cereal fiber, bran, and germ intake and the risks of all-cause and cardiovascular disease-specific mortality among women with type 2 diabetes mellitus. *Circulation* 2010;121:2162−2168.
12. Jacobs DR Jr, Meyer KA, Kushi LH, Folsom AR. Is whole grain intake associated with reduced total and cause-specific death rates in older

women? The Iowa Women's Health Study. *Am J Public Health* 1999;89:322−329.
13. Jacobs DR Jr, Meyer KA, Kushi LH, Folsom AR. Whole-grain intake may reduce the risk of ischemic heart disease death in postmenopausal women: the Iowa Women's Health Study. *Am J Clin Nutr* 1998;68: 248−257.
14. Jacobs DR Jr, Meyer HE, Solvoll K. Reduced mortality among whole grain bread eaters in men and women in the Norwegian County Study. *Eur J Clin Nutr* 2001;55:137−143.
15. Jacobs DR Jr, Andersen LF, Blomhoff R. Whole-grain consumption is associated with a reduced risk of noncardiovascular, noncancer death attributed to inflammatory diseases in the Iowa Women's Health Study. *Am J Clin Nutr* 2007;85:1606−1614.
16. Jensen MK, Koh-Banerjee P, Hu FB, Franz M, Sampson L, Gronbaek M, Rimm EB. Intakes of whole grains, bran, and germ and the risk of coronary heart disease in men. *Am J Clin Nutr* 2004;80:1492−1499.
17. Liu S, Stampfer MJ, Hu FB, Giovannucci E, Rimm E, Manson JE, Hennekens CH, Willett WC. Whole-grain consumption and risk of coronary heart disease: results from the Nurses' Health Study. *Am J Clin Nutr* 1999;70:412−419.
18. Liu S, Sesso HD, Manson JE, Willett WC, Buring JE. Is intake of breakfast cereals related to total and cause-specific mortality in men? *Am J Clin Nutr* 2003;77:594−599.
19. Lockheart MS, Steffen LM, Rebnord HM, Fimreite RL, Ringstad J, Thelle DS, Pedersen JI, Jacobs DR Jr. Dietary patterns, food groups and myocardial infarction: a case-control study. *Br J Nutr* 2007;98:380−387.
20. Oliveira A, Lopes C, Rodriguez-Artalejo F. Adherence to the Southern European Atlantic Diet and occurrence of nonfatal acute myocardial infarction. *Am J Clin Nutr* 2010;92:211−217.
21. Rautiainen S, Levitan EB, Orsini N, Akesson A, Morgenstern R, Mittleman MA, Wolk A. Total antioxidant capacity from diet and risk of myocardial infarction: a prospective cohort of women. *Am J Med* 2012;125:974−980.
22. Sahyoun NR, Jacques PF, Zhang XL, Juan W, McKeown NM. Whole-grain intake is inversely associated with the metabolic syndrome and mortality in older adults. *Am J Clin Nutr* 2006;83:124−131.
23. Steffen LM, Jacobs DR Jr, Stevens J, Shahar E, Carithers T, Folsom AR. Associations of whole-grain, refined-grain, and fruit and vegetable consumption with risks of all-cause mortality and incident coronary artery disease and ischemic stroke: the Atherosclerosis Risk in Communities (ARIC) Study. *Am J Clin Nutr* 2003;78:383−390.
24. Tavani A, Bertuzzi M, Gallus S, Negri E, La Vecchia C. Risk factors for non-fatal acute myocardial infarction in Italian women. *Prev Med* 2004;39:128−134.
25. Adom KK, Liu RH. Antioxidant activity of grains. *J Agric Food Chem* 2002;50:6182−6187.
26. Halvorsen BL, Holte K, Myhrstad MC, Barikmo I, Hvattum E, Remberg SF, Wold AB, Haffner K, Baugerod H, Andersen LF, Moskaug O, Jacobs DR Jr, Blomhoff R. A systematic screening of total antioxidants in dietary plants. *J Nutr* 2002;132:461−471.
27. Blomhoff R. Dietary antioxidants and cardiovascular disease. *Curr Opin Lipidol* 2005;16:47−54.
28. Dragland S, Senoo H, Wake K, Holte K, Blomhoff R. Several culinary and medicinal herbs are important sources of dietary antioxidants. *J Nutr* 2003;133:1286−1290.
29. Halvorsen BL, Carlsen MH, Phillips KM, Bohn SK, Holte K, Jacobs DR Jr, Blomhoff R. Content of redox-active compounds (ie, antioxidants) in foods consumed in the United States. *Am J Clin Nutr* 2006;84:95−135.
30. Lamming DW, Wood JG, Sinclair DA. Small molecules that regulate lifespan: evidence for xenohormesis. *Mol Microbiol* 2004;53: 1003−1009.