

## Effect of whole grains on markers of subclinical inflammation

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*The reduction of subclinical inflammation has been suggested as a potential mechanism to explain the favorable association between whole-grain consumption and reduced risk for cardiovascular disease, diabetes, and certain cancers. This review examines evidence for the effects of whole-grain consumption on markers of subclinical inflammation derived from 13 epidemiological and 5 interventional studies retrieved from a search of the PubMed database. Epidemiological studies provide reasonable support for an association between diets high in whole grains and lower C-reactive protein (CRP) concentrations. After adjusting for other dietary factors, each serving of whole grains is estimated to reduce CRP concentrations by approximately 7%. **In contrast to epidemiological studies, interventional studies do not demonstrate a clear effect of increased whole-grain consumption on CRP or other markers of inflammation.** Issues related to insufficient length of intervention, extent of dietary control, population selection, types of whole grains, and lack of a direct anti-inflammatory effect may underlie these discrepant findings. Additional carefully controlled interventional studies are needed to clarify the effects of whole grains on subclinical inflammation.*

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### INTRODUCTION

There is a substantial body of evidence supporting the association between higher whole-grain consumption and reduced risk for the development of major chronic diseases. Prospective population studies show that individuals who consume diets higher in whole grains have a reduced risk of developing cardiovascular disease,<sup>1-9</sup> type 2 diabetes,<sup>10-14</sup> and certain types of cancer.<sup>15-17</sup> Based in part on these favorable epidemiological findings, the US Department of Agriculture,<sup>18</sup> the American Heart Association,<sup>19</sup> and the American Diabetes Association<sup>20</sup> have recommended increased consumption of whole-grain foods.

The mechanisms by which whole grains exert their beneficial effects are not fully elucidated. However, the recognition that subclinical inflammation is associated with cardiovascular disease<sup>21</sup> and type 2 diabetes<sup>22,23</sup> has prompted investigations into the direct relationship between whole-grain intake and markers of subclinical

inflammation. Below, the evidence linking whole-grain consumption and subclinical inflammation is reviewed.

### SELECTION OF STUDIES FOR REVIEW

The PubMed database was searched (last search, May 2011) using the search string “(whole OR unrefined OR brown) AND (grain\* OR cereal\* OR wheat OR oat\* OR rye OR corn OR rice) AND (inflammat\* OR CRP OR C-reactive protein OR interleukin-6 OR IL-6) AND human\*.” The search yielded a total of 98 references. The retrieved articles were downloaded into a reference management database and the abstracts were reviewed for relevance. Only those studies that specifically examined whole grains in either epidemiological surveys (cross-sectional or prospective) or in dietary interventions were selected. Studies that primarily focused on whole-grain fractions such as fiber and/or bran products were excluded. Relevant papers were retrieved and their

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bibliographies were scanned to identify additional articles that may have been missed in the initial search. A total of 13 epidemiological studies<sup>24–36</sup> and 5 interventional studies were reviewed.<sup>37–41</sup> Within the epidemiological studies, a number of papers represented different analytical approaches or subpopulations using the same study population, including the Health Professionals Follow-Up Study,<sup>24,28</sup> the Nurses' Health Study,<sup>25,33</sup> and the Multi-Ethnic Study of Atherosclerosis.<sup>29,32,34</sup>

## MARKERS OF SUBCLINICAL INFLAMMATION

Epidemiological and interventional studies have used a number of circulating proteins as markers of subclinical inflammation, including C-reactive protein (CRP), interleukin-6 (IL-6), fibrinogen, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), and TNF- $\alpha$  receptor-1 and receptor-2. Of these, CRP is most commonly measured, followed by IL-6. CRP is an acute-phase protein secreted by the liver in response to IL-6.<sup>42</sup> Elevated concentrations of CRP are associated with increased risk for cardiovascular disease,<sup>43,44</sup> insulin resistance and type 2 diabetes,<sup>45</sup> and some cancers.<sup>44</sup> Similarly, elevated IL-6 concentrations are associated with increased risk for both cardiovascular disease<sup>46</sup> and type 2 diabetes.<sup>23</sup> A substantial amount of IL-6 is

produced by abdominal adipose tissue, which, in part, explains the relationship between obesity and subclinical inflammation.<sup>23,47</sup>

## DEFINING WHOLE-GRAIN FOODS

The FDA states that “cereal grains that consist of the intact, ground, cracked or flaked caryopsis [kernel], whose principal anatomical components – the starchy endosperm, germ, and bran – are present in the same relative proportions as they exist in the intact caryopsis – should be considered a whole grain.”<sup>48</sup> This definition allows for the grain to undergo processing, including the temporary separation of the individual components, as long as the final product contains the germ, endosperm, and bran in virtually the same proportion as the original grain. This definition differs from the operational definition of whole-grain foods used in epidemiological studies to estimate population intakes (Table 1). Because of the limitations associated with the range and description of food items contained within a food frequency questionnaire, items that do not meet the definition of a whole grain (e.g., wheat germ, wheat bran) or that may have very low or no whole-grain content (e.g., high-fiber breads and cereals) may be included in estimates of whole-grain intake. Conversely, other whole-grain items that may be

**Table 1** Definitions used to quantify whole-grain foods and serving sizes.

Study	Serving definition	Whole-grain foods definition
IRAS <sup>36</sup>	One serving defined as a participant-identified, medium-sized serving of FFQ line items comparable to servings consumed by men or women of the same age	Dark bread (including whole-wheat, rye, pumpernickel, and other high-fiber bread); high-fiber bran or granola cereals, shredded wheat; cooked cereal (including oatmeal, Cream of Wheat®, and grits) weighted by a factor of 0.5
MESA <sup>32</sup>	Patterned after the IRAS study	Cold cereal containing $\geq 3$ g dietary fiber per 100 g dry weight; oatmeal; dark, whole-grain breads or rolls; bran muffins; brown or wild rice
BioCycle <sup>35</sup>	A whole-grain serving defined as a 16 g or $\frac{1}{2}$ cup of a 100% whole-grain food	A food product in which a whole-grain ingredient was the first ingredient on the food label; products containing only some whole grains were not included
IWHS <sup>9</sup>	Commonly used serving size	Dark bread; cold breakfast cereal with $\geq 25\%$ whole grain or bran by weight; brown rice; popcorn; wheat germ; bran; cooked oatmeal, and other grains (bulgur, kasha, and couscous)
NHS <sup>25,33</sup> /HPFS <sup>24,28</sup>	Whole-grain intake reported in g/day, based on commonly used portion size and estimated percent whole-grain content derived from analysis of recipes and ingredient data	All foods that, based on analysis of average recipes and ingredient labels, contained any of the following: whole wheat and whole-wheat flour, whole oats and whole-oat flour, whole cornmeal and corn flour, brown rice and brown rice flour, whole barley, whole rye and rye flour, bulgur, buckwheat, popcorn, amaranth, and psyllium

*Abbreviations:* FFQ, food frequency questionnaire; HPFS, Health Professionals Follow-Up Study; IRAS, Insulin Resistance Atherosclerosis Study; IWHS, Iowa Women's Health Study; MESA, Multi-Ethnic Study of Atherosclerosis; NHS, Nurses' Health Study.

frequently (popcorn) or infrequently (bulgur/cracked wheat, kasha/buckwheat, barley) consumed are not included in other estimates. This poses challenges in identifying and quantifying the true effects of whole-grain intake on measured outcomes.

### COHORT STUDIES WITH DIETARY PATTERNS HIGH IN WHOLE GRAINS

The study of dietary patterns provides a comprehensive approach to the examination of the effects of diet on indices of health and disease. These dietary patterns can either be derived *de novo* from the diet intake data using principal components factor analysis (PCA) and reduced-ranked regression or be specified *a priori* on the basis of a pre-established dietary pattern (e.g., Dietary Approaches to Stop Hypertension [DASH] diet or Mediterranean diet). Of the five studies that derived dietary patterns *de novo* from the diet intake data, four showed reductions in CRP with increasing intake of a dietary pattern containing whole grains (Table 2). A study conducted in a subset of 732 women in the Nurses' Health Study<sup>25</sup> demonstrated a significant ( $P = 0.02$ ) inverse association between plasma concentrations of CRP and adherence to a dietary pattern derived by PCA and characterized by higher intakes of whole grains, fruits, vegetables, legumes, fish, and poultry. Similarly, a study of 5,089 participants in the Multi-Ethnic Study of Atherosclerosis<sup>29</sup> identified a dietary pattern by PCA that was characterized by higher intakes of whole-grain bread, rice and pasta, fruit, seeds, nuts and peanut butter, green leafy vegetables, and low-fat milk. Those in the upper quintile for consumption of this dietary pattern had a mean CRP concentration 21% lower than those in the lowest quintile of intake ( $P < 0.001$  for trend). A study conducted in 486 Iranian women<sup>31</sup> found that those who were in the highest quintile for consumption of a dietary pattern identified by PCA and characterized by increased intake of whole grains, fruits, vegetables, tomatoes, poultry, legumes, cruciferous and green leafy vegetables, tea, and fruit juices had a mean CRP concentration 29% lower ( $P < 0.01$  for trend) than those in the lowest quintile of consumption.

Using a somewhat different approach, Hoffmann et al.<sup>26</sup> derived a dietary pattern by reduced-ranked regression using 49 food groups on a food frequency questionnaire as potential predictor variables and low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, lipoprotein(a), CRP, and C-peptide as response variables. The data were derived from a population of 200 women with incident coronary artery disease and 255 age-matched controls. In the derived dietary pattern score, meat, poultry, margarine, vegetable fats and oils (except olive oil), and sauces were positively weighted, while vegetarian dishes, wine, cooked and raw vegetables,

and whole-grain cereals and muesli were negatively weighted. With increasing quintiles of the dietary score, whole-grain cereal and muesli consumption significantly ( $P < 0.0001$ ) decreased from 12 g/day to 4 g/day (1<sup>st</sup> versus 5<sup>th</sup> quintile), and CRP concentrations significantly ( $P < 0.0001$ ) increased from 7 mg/L to 32 mg/L.

Similarly favorable effects of prespecified dietary patterns containing whole grains have been demonstrated (Table 2). Thus, individuals consuming diets with the greatest characteristics of the DASH diet (increased whole grains, fruits, vegetables, nuts, legumes, low-fat dairy),<sup>33</sup> Mediterranean diet (increased nonrefined cereals and products, fruit, vegetables, olive oil, potatoes, fish),<sup>30</sup> a "Comprehensive Healthy Dietary Pattern" (higher in whole-grain bread, rice, cereal or pasta, fruit, seeds and nuts),<sup>34</sup> or who had a higher "Recommended Food Score" (higher in low-fat whole grains, low-fat dairy, lean meats, poultry, fish)<sup>27</sup> had plasma CRP concentrations that were approximately 10–20% lower in the highest versus the lowest quintile.

A number of these studies also examined effects on other markers of inflammation, including IL-6 and fibrinogen. Effects of increased consumption of diets rich in whole grains on these endpoints were slightly less consistent than the effects on CRP; for IL-6 concentrations, three studies<sup>29,33,34</sup> showed significant reductions and two studies<sup>25,31</sup> showed no effect, while for fibrinogen, one study<sup>30</sup> showed a favorable effect of dietary patterns rich in whole grains and another study<sup>34</sup> showed no effect.

Four studies examined the strength of the association between dietary patterns and CRP concentrations before and after covariate adjustments for indices of adiposity, with three studies<sup>29,31,34</sup> showing a weakened association and the other<sup>25</sup> a strengthened association. A weakening in the association between a dietary pattern and CRP concentrations would be consistent with at least part of the effects of the dietary pattern being mediated through changes in adiposity and/or adipose tissue metabolism.

Combined, these studies suggest that dietary patterns that include whole grains are associated with significant reductions in CRP concentrations and other markers of inflammation. Further, when comparing extremes in intakes of dietary patterns rich in whole grains, the extent of reduction in CRP is on the order of 10–29%. However, because these are complex dietary patterns containing many foods that have the potential to exert anti-inflammatory effects, the extent to which the observed reductions can be specifically attributable to whole-grain consumption cannot be stated with certainty.

### COHORT STUDIES OF WHOLE GRAINS

Four studies have specifically examined the association between whole-grain intake and markers of subclinical

**Table 2 Summary of cohort studies examining the effects of dietary patterns high in whole grains on CRP concentrations.**

Reference	Country	Cohort	Sex and no. of subjects	Dietary pattern with whole grains <sup>a</sup>	Model adjustments		CRP outcome across levels of dietary patterns <sup>d</sup>
					Base model <sup>b</sup>	Adiposity <sup>c</sup>	
Fung et al. (2001) <sup>24</sup> Lopez-Garcia et al. (2004) <sup>25</sup>	USA USA	HPFS NHS	M = 466 F = 732	Prudent diet factor <sup>e</sup> Prudent diet factor <sup>e</sup>	X X	X	NS trend across quintiles; NS regression coefficient P = 0.05 for negative trend across quintiles; NS regression coefficient
Hoffmann et al. (2004) <sup>26</sup>	Germany	CORA	F = 455	CAD diet factor <sup>f</sup>	X	X	P = 0.02 for regression coefficient ( $\beta = -0.10$ ) P < 0.0001 for positive trend across quintiles
Nettleton et al. (2006) <sup>29</sup>	USA	MESA	M = 2,407 F = 2,682	Whole grains and fruit factor <sup>e</sup>	X	X	P < 0.001 for negative trend across quintiles; P < 0.05 for regression coefficient ( $\beta = -0.089$ ) P < 0.05 for regression coefficient ( $\beta = -0.060$ ) P < 0.01 for negative trend across quintiles; P < 0.001 for regression coefficient ( $\beta = -0.090$ )
Esmailzadeh et al. (2007) <sup>31</sup>	Iran		F = 486	Healthy pattern factor <sup>e</sup>	X	X	P < 0.05 for negative trend across quintiles; P = 0.011 for regression coefficient ( $\beta = -0.050$ ) P = 0.02 for negative trend across quartiles
Kant et al. (2005) <sup>27</sup>	USA	NHANES III	M = 4,302 F = 4,358	Recommended food score <sup>e</sup>	X	X	P < 0.001 for regression coefficient ( $\beta = -0.27$ )
Panagiotakos et al. (2006) <sup>30</sup>	Greece	ATTICA	M = 1,514 F = 1,528	Mediterranean score <sup>e</sup>	X	X	P < 0.001 for negative trend across quintiles
Nettleton et al. (2008) <sup>34</sup>	USA	MESA	M + F = 5,042	Healthy pattern score <sup>e</sup>	X	X	P = 0.04 for negative trend across quintiles P = 0.008 for negative trend across quintiles
Fung et al. (2008) <sup>33</sup>	USA	NHS	F = 1,176	DASH score <sup>e</sup>	X	X	

<sup>a</sup> "Factor" designates analyses employing principal components or reduced-ranked regression to derive dietary patterns; "score" designates analyses employing prespecified dietary factors.

<sup>b</sup> Includes adjustments for any of the following: age, sex, race, education, smoking status, energy intake, physical activity, alcohol consumption, blood pressure, cholesterol concentrations, supplement use.

<sup>c</sup> Includes adjustments for any of the following: body mass index, waist circumference.

<sup>d</sup> NS, nonsignificant.

<sup>e</sup> Whole-grain intake increases with increasing quantile of score or factor.

<sup>f</sup> Whole-grain intake decreases with increasing quantile of score or factor.

Abbreviations: CORA, Coronary Risk Factor for Atherosclerosis in Women; CAD, coronary artery disease; CRP, C-reactive protein; HPFS, Health Professionals Follow-Up Study; MESA, Multi-Ethnic Study of Atherosclerosis; NHANES, National Health and Nutrition Examination Survey; NHS, Nurses' Health Study.

inflammation (Table 3). As previously mentioned, the definitions for whole-grain foods for inclusion in the analyses differed with each study. Nonetheless, in all four studies, in the least-adjusted statistical model, increased consumption of whole-grain foods was associated with a significant reduction in CRP concentrations ranging from 11% to 29% in a comparison of the first and last quantiles of whole-grain intake.<sup>28,32,35,36</sup> However, consistent with the dietary patterns analysis, individuals with higher whole-grain intakes generally had a healthier lifestyle, variably characterized by less smoking, lower body mass index (BMI), increased physical activity, increased fruit and vegetable intake, and decreased alcohol, saturated fat, and/or meat intake – not all of which were considered in the base statistical model. Consequently, after correcting for differences in BMI, waist circumference, and/or markers of insulin sensitivity or for other dietary components, including fruit, vegetables, refined grains, fiber, meat, and/or dietary fatty acids, the degree of association between whole-grain intake and CRP concentrations was substantially weakened<sup>32,36</sup> or became statistically nonsignificant.<sup>28,35</sup> Further, when both measures of adiposity/insulin resistance and confounding dietary variables were included in the model, no study revealed a significant independent effect of whole grains on CRP concentrations.

Similar results were found with other markers of inflammation. Two studies examined the association between whole-grain consumption and IL-6 concentrations, of which one showed no association<sup>28</sup> and the other showed a significant inverse association with the base model, but not for more fully adjusted models.<sup>32</sup> Two studies<sup>28,36</sup> also examined fibrinogen concentrations, with neither showing any significant association with whole-grain intake.

To obtain a quantitative estimate of the effect of a single serving of whole grains on CRP concentrations, published beta coefficients relating servings of whole-grain intake to log-transformed CRP concentrations were used. If beta coefficients were not provided, these values were estimated by regression analysis using quantile values for whole-grain intake and CRP concentrations. Whole-grain intake data expressed as grams per day were converted to servings per day by assuming that one whole-grain serving corresponded to 16 g of whole grains. Beta coefficients for the minimally adjusted base, diet-adjusted, adiposity/insulin resistance-adjusted, and/or fully adjusted models were included in a least-squares model that included whole-grain intake, study, and model adjustments as predictor variables. Data were weighted by the inverse of variance estimated for the beta coefficients.

The results of this analysis appear in Figure 1 and show that in the minimally adjusted model, each addi-

tional serving of whole grains reduces CRP concentrations by approximately 10%. As previously noted, whole-grain intake is associated with a healthier dietary pattern. Therefore, it is not surprising that after correction of any of a number of dietary covariates, the effect of whole grains is attenuated such that each additional serving is associated with a 7% reduction in CRP concentrations.

Adjustment of the model for measures of adiposity and/or insulin resistance further attenuates the effect of an additional serving of whole grains by approximately 40%, whether measured from the base or the diet-adjusted model. However, unlike adjustments for dietary covariates that serve to isolate the “true effect” of whole grains on CRP concentrations, adjustments for measures of adiposity in combination with insulin resistance provide information regarding potential mechanisms. Increased intake of whole grains is associated with reduced BMI and adiposity<sup>49</sup> and improved insulin sensitivity,<sup>50,51</sup> both of which have been shown to be associated with lower CRP concentrations.<sup>52–54</sup> Thus, approximately 40% of the improvement in CRP concentrations associated with increased whole-grain consumption may be due to the favorable effect of whole grain on adiposity and insulin sensitivity.

## INTERVENTIONAL STUDIES

In contrast to epidemiological studies, in which favorable effects of whole-grain consumption on inflammation are generally observed, data from interventional studies are much less conclusive. Of the five studies that specifically examined the effects of increased whole-grain intake, only one showed a significant favorable effect on CRP concentrations.

Andersson et al.<sup>37</sup> studied 30 participants (22 postmenopausal women and 8 men) between the ages of 35 and 70 years with at least one physiological marker of insulin resistance. Participants were instructed to include a fixed amount of refined-grain or whole-grain foods (112 g/day) in their habitual diet for a period of 6 weeks each, in a crossover design. The whole grains were a mixture of wheat, rye, oats, and rice, with wheat predominating. Relative to the end of the refined-grain period, consumption of whole grains was associated with a small but statistically significant increase in BMI, no change in insulin sensitivity, and no change in either CRP or IL-6 concentrations.

Similar results were observed in a smaller study of shorter duration. Fifteen participants (3 women, 12 men) with a mean age of 55 years and a mean BMI of 27.4 kg/m<sup>2</sup> were instructed to include refined- or whole-grain wheat products into their habitual diet for a period of 3 weeks each. No significant effects of inclusion of

**Table 3 Summary of cohort studies examining effects whole grains on CRP concentrations in healthy adults.**

Reference	Cohort	Sex and no. of subjects	Whole-grain intake (first versus last quantile)	Model adjustments			Outcome <sup>d</sup>
				Base model <sup>a</sup>	Adiposity/insulin resistance <sup>b</sup>	Diet <sup>c</sup>	
Jensen et al. (2006) <sup>28</sup>	HPFS & NHS II	M = 468 F = 470	8.2 versus 43.8 g/day	X			P = 0.03 for negative trend across quintiles
Lutsey et al. (2007) <sup>32</sup>	MESA	M + F = 5,496	0.02 versus 1.39 servings/day	X	X		NS trend across quintiles
				X	X	X	NS trend across quintiles P < 0.0001 for negative trend across quintiles
Masters et al. (2010) <sup>36</sup>	IRAS	M + F = 940	0.04 versus 2.00 servings/day	X		X	P = 0.004 for negative trend across quintiles NS trend across quintiles
				X	X	X	P = 0.0181 for regression coefficient ( $\beta = -0.103$ )
Gaskins et al. (2010) <sup>35</sup>	BioCycle	F = 249	None versus 1.6 servings/day	X	X		P < 0.034 for regression coefficient ( $\beta = -0.102$ ) NS for regression coefficient ( $\beta = -0.036$ )
				X	X	X	P = 0.04 comparing none versus $\geq 1$ serving/day NS comparing none versus $\geq 1$ serving/day

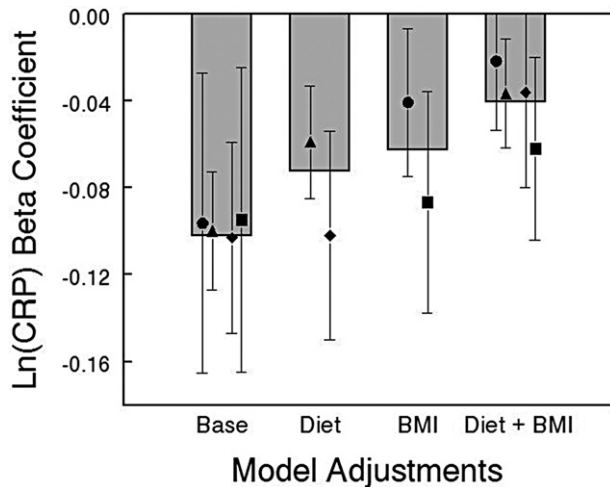
<sup>a</sup> Includes adjustments for any of the following: age, sex, race, education, smoking status, energy intake, physical activity, alcohol consumption, cholesterol concentrations.

<sup>b</sup> Includes adjustments for any of the following: BMI, waist circumference, insulin concentrations, insulin sensitivity (SI), 2h-postprandial glucose.

<sup>c</sup> Includes adjustments for any of the following intakes: fruit, vegetables, refined grains, fiber, fish and poultry, meat, fatty acid class.

<sup>d</sup> NS, nonsignificant.

Abbreviations: HPFS, Health Professionals Follow-Up Study; IRAS, Insulin Resistance Atherosclerosis Study; MESA, Multi-Ethnic Study of Atherosclerosis; NHS II, Nurses' Health Study II.



**Figure 1 Beta coefficients relating change in log-transformed CRP [Ln(CRP)] per serving of whole grains.** The “Base” model is the minimally adjusted model that does not include adjustments for dietary factors (other than energy), measures of adiposity, or measures of insulin resistance. The “Diet” adjusted model includes adjustments for any of the following intakes: fruit, vegetables, refined grains, fiber, fish and poultry, meat, fatty acid classes. The “BMI” adjusted model includes adjustments for any of the following: BMI, waist circumference, insulin concentrations, insulin sensitivity (Si), 2h-postprandial glucose. Data from individual studies are displayed as symbols with error bars (mean  $\pm$  SE), with common symbols across adjustment models representing the same study. Bars represent estimates of the beta coefficient for each model, based on analysis of the composite study data.

whole-wheat products into the diet were observed on either insulin sensitivity or CRP concentrations.<sup>40</sup>

The WHOLEheart study<sup>39</sup> is the largest interventional study conducted to date to examine the effects of whole-grain supplementation. A total of 316 participants, with low habitual consumption of whole-grain foods and BMIs above 25 kg/m<sup>2</sup>, were randomized to one of three diet groups. The control group was asked to maintain their current dietary habits. The intervention groups were provided with a range of whole-grain products and were instructed to substitute the products for similar items in their habitual diet. One group was instructed to increase their consumption of whole grains to 60 g/day for a total of 16 weeks, while a second group was instructed to increase their consumption of whole grains to 60 g/day for the first 8 weeks and to 120 g/day for the final 8 weeks. At the end of the 16-week study, no significant differences were observed in the concentrations of either CRP or IL-6.

Another large study examined the effects of whole grains in 226 overweight (mean BMI of intervention

groups, 27.0–28.0 kg/m<sup>2</sup>) middle-aged men and women.<sup>41</sup> After a 4-week run-in period in which participants consumed a refined-grain (habitual) diet, they were randomized to one of three interventions: a refined-grain diet, a prescribed diet in which regular refined-grain food items were replaced with three servings of whole-wheat foods, or a prescribed diet in which refined grains were replaced with one serving of whole-wheat foods and two servings of oats. At the end of the 12-week intervention, changes from the run-in diet for CRP or IL-6 concentrations were not significantly different between diets.

A favorable effect of increased whole-grain consumption on subclinical inflammation was identified when subjects were provided with a hypocaloric diet.<sup>38</sup> Fifty obese participants with a mean age of 46 years and a BMI > 30 kg/m<sup>2</sup> received dietary advice to either avoid all whole-grain foods or consume only whole-grain foods for a period of 12 weeks. Dietary advice to both groups also included a 500 kcal/day deficit. The whole-grain group increased whole-grain intake to approximately five servings per day. At the end of the intervention, there was no difference in weight loss between groups, although the whole-grain group lost a significantly greater percentage of body fat in the abdominal region. Additionally, CRP concentrations declined significantly by 38% in the whole-grain group but were unchanged in the refined-grain group. Changes in CRP concentrations were not correlated with the extent of weight loss, suggesting a mechanism of action independent of effects on adiposity.

Several reasons may explain why interventional studies have not consistently confirmed the favorable effects of increased whole-grain consumption on subclinical inflammation that have been observed in epidemiological studies. First, in none of the studies was diet completely controlled. Systematic or random day-to-day variations in dietary constituents that have the potential to impact markers of inflammation (dietary fatty acids, glycemic load, antioxidants), combined with the inappropriate substitution of foods in the habitual diet with the intervention foods, would make the identification of any true effects of whole grains more problematic. As an example, in the WHOLEheart study, the inclusion of whole grains in the diet was accompanied by a reduction in fruit consumption,<sup>39</sup> which may have offset any anti-inflammatory effects of whole grains. Additionally, in the WHOLEheart study, it was noted that energy intake increased in the whole-grain groups, suggesting that the supplied food items were added on top of, rather than substituted for, similar items in the regular diet. A similar incomplete substitution may have occurred in the study by Andersson et al.,<sup>37</sup> since it was observed that BMI values were slightly but significantly higher after consumption of whole-grain versus refined-grain products.

Participant selection may be an additional confounding issue. In all of the interventional studies, participants were selected on the basis of being either overweight or obese. On the surface, this may seem like a reasonable selection criterion given that overweight and obese individuals are more likely to have elevated markers of subclinical inflammation and thus would appear to be more amenable to the potentially favorable anti-inflammatory effects of whole grains. However, in a study examining the effects of a high-fiber DASH diet (which included whole grains), significant reductions in CRP concentrations were seen only in lean participants (30% drop) as opposed to obese participants (10% drop).<sup>55</sup> This may also explain the favorable effects of whole grains on CRP concentrations when combined with weight loss and abdominal fat loss.<sup>38</sup>

Additional study design elements may also underlie the lack of observed effect of whole-grain consumption on markers of inflammation. Observational studies examine the effects of dietary constituents consumed over a period of several years in several hundred to several thousand individuals. In contrast, interventional studies are conducted over a period of weeks to several months and involve far fewer individuals. Thus, if the effects of whole grains take a long time to manifest themselves and/or the effect size is relatively small, then the design limitations typically associated with interventional studies may make it difficult to detect the effects of whole grains on inflammatory markers.

Finally, one must also concede the possibility that the effects of whole grains on subclinical inflammation observed in observational studies are due to residual confounding with other lifestyle and dietary factors, and that whole grains do not independently contribute to reductions in subclinical inflammation.

#### **POTENTIAL IMPACT OF REDUCTION IN CRP, ACHIEVED THROUGH INCREASED WHOLE-GRAIN CONSUMPTION, ON RISK OF CARDIOVASCULAR DISEASE**

Estimates from epidemiological studies suggest that each serving of whole grains is associated with approximately a 7.2% reduction in CRP concentrations. Thus, CRP concentrations would be expected to decline by 20% if one were to consume the recommended amount of whole grains (50% of 6 servings of grains). Meta-analysis of 31 long-term prospective studies<sup>44</sup> suggests a relative risk for coronary heart disease of 1.37 for each 1.1 increase in natural logarithm CRP concentrations (corresponding to a 3-fold change in CRP concentrations). Translating this relationship to the decline in CRP associated with three servings of whole grains predicts reductions in the risk of coronary heart disease of approximately 6%. In contrast, epidemiological studies<sup>3,4,8</sup> suggest that an increase of

three servings of whole grains decreases the risk of coronary heart disease by 15–25%. Thus, only a fraction of the reduction in cardiovascular disease risk associated with increased whole-grain consumption is likely to be mediated by changes in CRP concentrations.

#### **CONCLUSION**

Prospective epidemiological data provide a reasonable body of evidence pointing towards a modest effect of whole grains to reduce markers of subclinical inflammation, especially circulating concentrations of CRP. However, results from the epidemiological studies should be interpreted with caution, given that definitions used to define “whole-grain foods” differ substantially across studies and can either include products that do not meet the definition of whole grains (e.g., bran cereals) or exclude potentially important sources of whole grains (e.g., brown rice and popcorn). Thus, the true effects of whole-grain consumption may be either higher or lower than currently estimated.

Interventional studies have the potential to provide the clearest understanding of the effects of whole grains on subclinical inflammation. However, studies conducted to date have not provided clear evidence of an effect of whole grains on any of a number of markers of inflammation and thus are largely in contrast with the observational studies. As has been previously addressed,<sup>56</sup> future interventional studies must be robustly designed to identify potential favorable effects of whole-grain consumption on markers of subclinical inflammation. The interventional studies must be adequately powered and of sufficient length to identify potential long-term effects. Ideally, the dietary intervention should be rigorously controlled through the provision of all meals. The characteristics of the selected study population should be carefully considered to ensure that the results are generalizable. Finally, study designs should additionally take into consideration the possibility that all whole grains are not equal with respect to their health-promoting characteristics. Given that wheat, corn, rye, rice, and oats differ substantially with respect to their carbohydrate, fiber, and phytochemical composition,<sup>57–59</sup> it is likely naive to assume that they all share the same physiological properties. It is well known that wheat and oat products differ substantially with respect to their ability to influence low-density lipoprotein cholesterol concentrations,<sup>60,61</sup> and preclinical studies in mice have shown that whole grains differ with respect to their metabolic properties.<sup>62,63</sup>

Given the importance of subclinical inflammation as a risk factor for chronic disease and the substantial role that grain and cereal products play in the food supply, it is important to gain a better understanding of the potential for whole grains to reduce inflammation. Knowledge of



the relative effects of individual types of whole grains, the components within whole grains that confer any anti-inflammatory properties, and the mechanism of action of such components would be of value to both the food industry and the public in efforts to provide a more healthful diet. Additional research, employing well-controlled dietary interventions, should be directed towards these areas.

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