factors,[1,2] but no consistent relation with the risk of CHD has been found.[3] Thus, in our study[4] we did not think about ferritin level as a potential confounder. An important interpretation of our results is that the risk in women seems to be unrelated to menopausal status or to any factors related to menopausal status. There appears to be no protection of being premenopausal vs postmenopausal above what can be explained by a difference in age. The declining relative risk for sex with increasing age seems to be a consequence of a more pronounced flattening of risk level changes in middle-aged men, approaching the risk level for women. This is in contrast to previous beliefs that the risk in women approximate the risk level for men at a certain age. As Mascitelli and Goldstein point out, the absolute risk of MI in women increases about a decade after normal menopausal age. However, an even steeper increase in risk is seen in men, leading to increasing sex differences in absolute risk with increasing age. It is thus difficult to explain the age incidence patterns in view of sex differences in ferritin levels. In a Danish population study[5] with follow-up through 1991, standardized age incidence curves were rather parallel for men and women (log-linear scale), in apparent contrast to the age- and sex-related changes in body iron stores.

In addition to increasing oxidative stress, increased iron stores have been suggested to promote CHD by alteration of endothelial function, decreased vascular reactivity, and reperfusion injury by iron-induced free radicals.[6] Different markers of body iron status have been used for testing the iron-heart hypothesis in humans. Despite initial positive findings from experimental and preclinical research, conflicting results have emerged from epidemiological studies.[3,6] The only large randomized clinical trial that assessed the effect of iron-store reduction by phlebotomy in patients with peripheral arterial disease found no significant association with all-cause mortality or MI.[7] Mascitelli and Goldstein refer to results from age-specific analyses of data from this study. A positive effect of reduction in body iron stores were found only among persons in the lowest age quartile. Although the ferritin hypothesis is fascinating and has generated much research, there is no strong evidence for an association between body iron stores and risk of CHD. It is therefore less likely that body iron can explain the contrast in risk between sexes. However, body iron has been suggested to act synergistically with hypercholesterolemia.[3,6] Thus, it is possible that ferritin levels act as effect modifier on the association with established CHD risk factors, and that sex differences in ferritin levels lead to sex heterogeneity in the association with these factors unless adjusted for in the analysis. Interaction effects involving body iron are not yet fully explored.

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Lingering Questions Concerning Specific Dietary Fats and Mortality

To the Editor In a recent issue of *JAMA Internal Medicine*, Wang et al,[1] in their Letter in Reply to a Letter to the Editor by Ravnskov et al,[2] reiterate that their analysis is superior to that of other epidemiologists who find no correlation between saturated fat and mortality. However, there remain some serious questions about their study that it would help to have answered.

First, in the 1980 baseline data for the Nurses' Health Study (NHS),[3] the average energy intake reported is approximately 1500 kcal/d.[3] This seems to indicate underreporting on the order of approximately 20% energy from the largest of the 2 cohorts. How is it then possible to make predictions about the replacement of 1% or 5% of energy within these cohorts with any accuracy, let alone extrapolate this to the wider public in the form of claims and recommendations about diet and health?

Second, in the raw data for the NHS cohort[3] (eTable 3 in the Supplement), total deaths in the lowest quintile for saturated fat intake number 5660, more than double the number of deaths in the highest quintile, 2332. Can the authors explain why a strong association in favor of saturated fat was reversed on adjustment for age when the age difference between quintiles was only 2.3 years?

Third, the finding that the highest quintile of saturated fat intake had an increased risk of mortality from respiratory disease (hazard ratio [HR], 1.56; 95% CI, 1.30-1.87), is, as Wang et al[3] correctly state, novel and unsupported. Respiratory mortality is usually associated with smoking.[4] Does this finding indicate residual confounding due to the underreporting of smoking by health professionals?

Finally, why did Wang et al[3] recommend the consumption of polyunsaturated vegetable oils and spreads in Harvard Chan press releases[5] when their study did not confirm that these were the food sources of polyunsaturated fat associated with benefit?

Poultry, pork, and nuts are also major sources of linoleic acid, whereas α-linolenic acid in the US diet is mainly sourced from 2 oils—soy and canola. α-Linolenic acid was associated with cancer mortality (HR, 1.12; 95% CI, 1.04, 1.20) (eTable 14 in the Supplement).[3] It is an unusual proceeding for epidemiologists to recommend increasing intake of a nutrient they have found to be associated with cancer.

We recommend authors apply the Bradford Hill criteria as a tool for determining the likelihood of causation from epidemiological evidence.[6] Incomplete and inconsistent evidence, and weak associations, in the light of contradictory evidence from other investigations into the same questions, do not support the public health recommendations these authors are making.

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Conflict of Interest Disclosures: Dr Schofield is a coauthor of the *What The Fat?* series of books on diet and health. No other conflicts are reported.

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In Reply Schofield and Henderson cited the lower energy intake measured by food frequency questionnaires (FFQs) to question the validity of our findings.[1] It is well known that energy intake is underestimated by FFQs due to a limited number of foods. However, owing to correlated errors between intakes of energy and macronutrients, calculating fatty acid intake as percent of energy will largely cancel out the errors.[2] Furthermore, the validity and reliability of FFQ-measured dietary fatty acids (as percent of energy) have been extensively documented.[2]

Schofield and Henderson raised a question about the age-adjusted association between saturated fatty acid (SFA) intake and mortality in the Nurses' Health Study. Notably, the 2.3-year difference in age across quintiles of SFA intake in Table 1 was for baseline only.[1] All the variables (except those indicated as baseline variables), including diet and age, were updated every 2 to 4 years. During the follow-up, older participants reduced more SFA intake than their younger counterparts. Consequently, participants in the lowest quintile of SFA intake were much older than those in the highest quintile (mean difference, approximately 15 years), resulting in a strong confounding by age.

Contrary to the assertion by Schofield and Henderson, our previous studies have demonstrated that self-reported smoking is highly reliable,[3] and self-reported smoking strongly predicted lung cancer incidence.[4] Furthermore, our analysis adjusted for both baseline and updated smoking status in very fine categories. We also found a significant positive association between SFA intake and respiratory disease mortality among never-smokers (hazard ratio for substituting 5% of energy from carbohydrates by the same energy from SFA, 1.36; 95% CI, 1.00-1.85) despite the small number of respiratory disease deaths in this subgroup. Thus, the hypothesized residual confounding due to underreport of smoking is unlikely to explain our findings.

Plant oils have much higher amounts of polyunsaturated fatty acids (PUFA) than animal foods. For example, 100 g of cooked beef contains 0.43 g PUFA, whereas 100 g of soybean oil contains 57.7 g PUFA in the US Food Composition Databases. Given the benefits of replacing SFA by PUFA, recommending the replacement of high-SFA foods by high-PUFA foods is a sound population-wide approach to improving diet quality. Although α-linolenic acid intake was associated with slightly higher cancer mortality, we did not consider this association robust because it became nonsignificant in the sensitivity analysis that examined recent intake.

In contrast to the claim by Schofield and Henderson, our study[1] provided strong evidence because of many repeated measurements of diet, validated measurement methods, and high follow-up rates over decades. More important, our analysis was able to directly compare SFA with other macronutrients in an isocaloric manner. Our findings are consistent with other high-quality evidence, such as a pooled analysis of cohort studies that explicitly specified the comparison nutrients[5] and meta-analyses summarizing effects of replacing SFA by PUFA on both blood lipids[6] and cardiovascular disease[7] in randomized trials. Overall, current evidence meets key Bradford-Hill criteria with regard to the strength and consistency of the evidence, biological plausibility, temporal relationships, and experimental evidence on intermediate biomarkers.

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Incorrect Conclusions Concerning Antibiotics and Asthma Exacerbation

To the Editor We strongly support antibiotic stewardship, but we disagree with the statement, "Johnston and colleagues[1] demonstrate that antibiotics for asthma exacerbation do not improve outcomes,"[2(p1649)] from an Invited Commentary by Mehrotra and Linder in a recent issue of *JAMA Internal Medicine*. It is true that the AZALEA study[1] showed no benefit in primary or secondary outcomes; however, the statement by Mehrotra and Linder[2] is not supported by the data we reported.

AZALEA[1] studied azithromycin in adults, more than 99% of whom were in secondary care,[1] so the conclusions cannot be generalized to other antibiotics, other settings, or to children. Additionally of 4582 patients screened, only 199 were randomized, again limiting generalizability. AZALEA[1] was also underpowered, as 199 of a planned 380 patients were randomized, and a significant treatment effect in favor of azithromycin could not be confidently excluded. Finally, the major reason for nonrecruitment was antibiotic receipt before screening (2044 screened patients were excluded for this reason), thus for each patient randomized, more than 10 patients failed screening because they had already received antibiotics.

Such unexpectedly high antibiotic usage likely influenced study outcomes because patients who might have benefitted from antibiotic therapy for their asthma exacerbation were likely excluded from the study through already having received antibiotics. Patients being screened had often been seen by 3 independent physicians and/or teams (primary care, emergency department, and on-call respiratory and/or medical care physicians) who had assessed them for suitability for antibiotics prior to screening. As a result, those not prescribed antibiotics and therefore eligible for randomization were likely negatively selected against for suitability for antibiotics.

Thus, we do not agree with the statement in question.[2] Other studies that have reported benefit with antibiotics can be observed,[3,4] and we echo the call from Brusselle and Van Braeckel in their balanced and excellent Editorial[5] for further trials in primary and secondary care to investigate which patients with asthma attacks might benefit from antibiotic treatment.

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In Reply The focus of our Invited Commentary[1] was on antibiotic stewardship and we did not go into either the details of the AZALEA trial[2] nor its generalizability. The single sentence summary of the AZALEA trial[2] in our article[1] potentially oversimplifies the findings of the study by Johnston and colleagues. However, we respectfully disagree with Johnston and colleagues that our interpretation of their trial[2] was inaccurate. Our summary of the AZALEA trial[2] was consistent with the brief summary provided by *JAMA Internal Medicine* that stated, "This randomized clinical trial found no statistically or clinically significant benefit in symptoms, lung function, or speed of recovery." Brusselle and Van Braeckel stated, "…addition of azithromycin to standard medical care for acute asthma exacerbations did not result in a statistically or clinically significant benefit."[3(p1637)]

Current guidelines note that the role of bacterial infection in asthma exacerbation has been exaggerated and discourage use of antibiotics.[4] Of course there is a possibility that in the future we might identify a subgroup of patients with an asthma exacerbation who might benefit from antibiotics. But for now the answer is clear in terms of clinical practice: antibiotics should not be a standard component of asthma exacerbation treatment.

As the AZALEA trial[2] unfortunately demonstrated, there is gross overuse of antibiotics for asthma exacerbations. Such antibiotic use exposes patients to the harms of antibiotics—including minor reactions like rashes and yeast infections, more severe allergic reactions, and *Clostridium difficile* infection—with no apparent clinical benefit. As we discussed in our