A recent article in the Archives examined the extent to which 4 healthy lifestyle factors and their combinations were associated with reduced risk of developing chronic diseases. In the European Prospective Investigation Into Cancer and Nutrition (EPIC)-Potsdam study, compared with participants with no healthy factors, those with all 4 healthy factors had reductions of 93% (95% confidence interval [CI], 88% to 95%) for diabetes (P value for linear trend, <.001); 81% (95% CI, 47% to 93%) for myocardial infarction (MI) (P value for linear trend, <.001); 50% (95% CI, 18% to 79%) for stroke (P value for linear trend, .054); and 36% (95% CI, 5% to 57%) for cancer (P value for linear trend, <.001). As suggested by Ford et al., further studies in other populations are needed to evaluate the extent to which chronic disease may be potentially preventable.

Methods. The Blue Mountains Eye Study (BMES-1) is a population-based cohort study of sensory loss and other health outcomes, with methods previously reported. During 1992 to 1994, 3654 participants 49 years or older were examined (82.4% participation). At the 5-year follow-up examinations (BMES-2), 2335 surviving participants (75.1% of survivors; 543 had died) were examined. Of the 2335 survivors in the BMES-2, 1952 (75.6% of survivors; 1103 persons died) were re-examined at the 10-year follow-up examinations (BMES-3).

Incident disease outcomes were assessed using the same definitions as in the EPIC-Potsdam report. Similarly, we used the same 4 healthy factors and methods to form an index ranging from 0 to 4, as detailed by Ford et al. However, because our physical activity measures were not available in hours per week, we included a definition of engaging in physical activity as 3 times/wk or more. The covariates adjusted for in incidence analyses included age, sex, educational status (having/not having tertiary qualifications), and occupational status (employed or unemployed).

Results. Of the 3654 participants at baseline, 2639 had information on all 4 healthy factors. As in EPIC-Potsdam, participants who had diabetes (n=208 [7.9%]), MI (n=219 [8.3%]), stroke (n=84 [10.9%]), and cancer (n=189 [7.2%]) at baseline were excluded from analyses. Of the remaining participants, 50.0% had a healthy diet score, 82.5% had a body mass index lower than 30 (calculated as weight in kilograms divided by height in meters squared), 48.2% had never smoked, and 44.1% had participated in physical activity at least 3 times/wk. After adjusting for age, sex, and educational and occupational status, the risk of developing incident diabetes (P value for linear trend, <.001) and MI (P value for linear trend, <.001) decreased as the number of healthy lifestyle factors increased (Table), but this was not observed for incident stroke. Having 1 or more healthful factors compared with 0 factors did not lower the risk of incident MI and stroke. However, having all 4 healthy lifestyle factors had the greatest impact on incident diabetes—an 83% risk reduction.

Comment. In our older population, a slightly higher proportion (11.4%) of participants than in the EPIC-Potsdam study (9.1%) adhered to all 4 healthful factors. The BMES participants with all 4 healthy lifestyle factors had an 83% reduced risk of incident diabetes, and a significant linear trend was observed for incident MI, reinforcing the findings by Ford et al.

<table>
<thead>
<tr>
<th>Healthy Behaviors, No.</th>
<th>Participants, No. (%)</th>
<th>Diabetes (n=143 [8.5%])</th>
<th>Myocardial Infarction (n=362 [18.6%])</th>
<th>Stroke (n=187 [9.5%])</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>77 (2.9)</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>1</td>
<td>570 (21.6)</td>
<td>0.42 (0.20-0.90)</td>
<td>1.11 (0.55-2.27)</td>
<td>1.37 (0.46-4.10)</td>
</tr>
<tr>
<td>2</td>
<td>915 (34.7)</td>
<td>0.28 (0.13-0.60)</td>
<td>0.68 (0.34-1.38)</td>
<td>1.06 (0.36-3.12)</td>
</tr>
<tr>
<td>3</td>
<td>775 (29.4)</td>
<td>0.22 (0.11-0.48)</td>
<td>0.64 (0.31-1.29)</td>
<td>1.21 (0.41-3.56)</td>
</tr>
<tr>
<td>4</td>
<td>302 (11.4)</td>
<td>0.17 (0.07-0.42)</td>
<td>0.51 (0.23-1.01)</td>
<td>0.98 (0.31-3.06)</td>
</tr>
</tbody>
</table>

* Adjusted for age, sex, educational status, and occupational status.

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In contrast, having all 4 healthy lifestyle factors among the BMES participants did not significantly reduce the risk of incident stroke. As recommended by Katz et al, retirement of dietary quality (eg, including fish consumption, lean vs fattier meats) may have strengthened observed associations between lifestyle and health outcomes in our study. Nevertheless, our findings in a population older than those in the EPIC-Potsdam study concur with its take-home message, and that from other prospective studies that healthful dietary and lifestyle factors are beneficial in reducing the risk of developing chronic diseases, particularly diabetes.

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COMMENTS AND OPINIONS

Risk of Thiazolidinedione-Associated Fracture Should Be Appropriately Assessed

In the August 10/24 issue of the Archives, Dormuth et al reported an increased fracture rate in provincially insured residents of British Columbia, Canada, exposed to thiazolidinediones between January 1998 and December 2007. We wish to comment on several statements in the article.

Dormuth et al described their study as a prospective cohort study, when in fact it was a retrospective database analysis. It is well recognized that prospective studies offer a higher probability of detecting true associations than retrospective studies because they allow greater control to be exercised over confounding factors and data collection. We do not mean to question the validity of the results of their analysis but to suggest that the data should be interpreted in the context of the retrospective study design used.

The authors stated that most nonperipheral fractures in our female cohort members who received pioglitazone occurred in the spine, which could indicate an association between pioglitazone and spinal fractures. . . .

The 5 spine fractures seen with pioglitazone use in women in their study represented an incidence of 0.278 per 100 patient-years, compared with 0.242 per 100 patient-years for sulfonylureas. The statement of a potential association is unwarranted by an apparent difference of 0.036 per 100 patient-years detected in a retrospective analysis.

Dormuth et al stated several times that fracture data from the pioglitazone PROActive trial (PROspective pioglitAzone Clinical Trial In macroVascular Events), the long-term, placebo-controlled, prospective cardiovascular events trial in patients with type 2 diabetes and established macrovascular disease, have not been published. However, these data were published in the March 2009 issue of Drug Safety. As reported in the pioglitazone labeling and in a “Dear Healthcare Provider” letter in March 2007, the PROActive results showed an increased fracture risk in women but not in men. Among women, the incidence of fracture was 5.1% (44 of 870) for pioglitazone compared with 2.5% (23 of 905) for placebo; the excess risk associated with pioglitazone was 0.5 fractures per 100 patient-years. The majority of fractures were in the distal upper or lower limb. In men, the fracture incidence was 1.7% (30 of 1735) for pioglitazone and 2.1% (37 of 1728) for placebo. This finding is in contrast to the adjusted hazard ratio reported by Dormuth et al of 1.36 for any fracture in men receiving pioglitazone compared with sulfonylureas. Furthermore, the mean follow-up in the PROActive trial was more than 1000 days (34.5 months), compared with the mean thiazolidinedione exposure of 460 days in the retrospective analysis reported by Dormuth et al.

Dormuth et al appropriately pointed out that, “The association between pioglitazone and fractures in men must therefore be viewed as a basis for further research rather than as a definitive result.” They concluded, however, that there is insufficient clinical trial evidence to show that treatment with thiazolidinediones provides clinical benefits beyond glycemic control, and in the absence of mitigating clinical benefits, mounting evidence of harm should discourage physicians from prescribing those drugs.

In addition to glycemic control, the benefits of pioglitazone treatment include the reduced risk of adverse cardiovascular events demonstrated by the