THE AUTHORS REPLY: Dr. Schwartz correctly notes that the majority of the participants in the Women's Health Study were at low risk for coronary heart disease, as measured by the Framingham risk score. However, 1100 participants did have a risk of coronary heart disease that was 10 percent or greater. Among these high-risk participants, the findings were consistent with the overall findings of the trial, with no significant benefit with respect to the primary end point of major cardiovascular events for women taking aspirin as compared with those taking placebo (61 events in the aspirin group and 60 in the placebo group, P=0.74); there was a benefit for total stroke (17 events vs. 32, respectively; P=0.04) and a trend toward benefit for ischemic stroke (16 vs. 29, P=0.07), and there was no benefit for myocardial infarction (32 vs. 23, P=0.15). Thus, although overall the population had a low risk of cardiovascular events, it is important to note that there was no evidence of a modification of the effect of aspirin according to levels of the Framingham risk score in our study.

Dr. Dalen is correct in pointing out that our trial demonstrated that the specific dose of 100 mg of aspirin every other day was not associated with a reduction in myocardial infarction overall, and he raises the important question of whether this very low dose was inadequate to produce a cardioprotective effect in women. Although we agree that it is certainly possible that the dose was inadequate, there was no direct evidence to support this in the Women's Health Study. We showed that levels of thromboxane and prostacyclin were reduced with 100 mg of aspirin every other day; we observed the expected increased risk of gastrointestinal bleeding, hemorrhagic stroke, nongastrointestinal bleeding, and peptic ulcer, and 100 mg every other day was adequate both to lower the risk of stroke overall and to lower the risk of myocardial infarction as well as stroke in women 65 years of age or older. However, the issue of the lowest effective dose in both women and men requires further research.

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The Ubiquilin 1 Gene and Alzheimer's Disease

TO THE EDITOR: Bertram et al. (March 3 issue)[1] report that in two family-based cohorts, a genetic variant of the UBQ-8i single-nucleotide polymorphism on chromosome 9q22 putatively increased the risk of Alzheimer's disease in an additive disease model. We attempted replication in a similarly ascertained but independent family-based data set based on 288 families in which linkage to microsatellites at 9q22.1 and 9q34.2 was demonstrated in a genome scan.[2] In addition, we analyzed a previously described independent data set based on patients with Alzheimer's disease and 1005 controls.[3]

We found no association between the risk of Alzheimer's disease and UBQ-8i, or any of six additional single-nucleotide polymorphisms within the *UBQLN1* gene, in either of the independent data sets. However, using age at onset as the trait of interest, we found a significant association between the putative UBQ-8i risk allele and an older age at onset in a recessive-disease model only in our case–control data set (Table 1). We found an additional, significant effect related to age at onset only in our family-based data set with a different single-nucleotide polymorphism in *UBQLN1*. Thus, although we found no evidence of risk with any single-nucleotide polymorphism in *UBQLN1*, our results suggest that age at onset may be germane and that additional, detailed examination of *UBQLN1*, including a search for the functional variant (or variants), is warranted.

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1. Bertram L, Hiltunen M, Parkinson BS, et al. Family-based association between Alzheimer's disease and variants in *UBQLN1*. N Engl J Med 2005;352:884-94.
2. Pericak-Vance MA, Grubber J, Bailey LR, et al. Identification of novel genes in late-onset Alzheimer's disease. Exp Gerontol 2000;35:1343-52.
3. van der Walt JM, Dementieva YA, Martin ER, et al. Analysis of European mitochondrial haplogroups with Alzheimer disease risk. Neurosci Lett 2004;365:28-32.

Table 1. UBQ-8i Allelic Associations.*

Analysis	Family-Based Data Set†		Patient–Control Data Set‡	
	Test§	P Value	Test	P Value
Risk analysis	Family-Based Association Test	0.87	Logistic regression (additive model)	0.23
	Pedigree Disequilibrium Test	0.96		
Analysis of age at onset	Quantitative Transmission Disequilibrium Test	0.21	Linear regression (recessive model)	0.01

* All the patients with Alzheimer's disease met the National Institute of Neurological Disorders and Stroke/Alzheimer's Disease and Related Disorder Association case definition and were evaluated at Duke University Medical Center and Vanderbilt University Medical Center through the collaborative Alzheimer Project.
† In the family-based data set, the mean (±SD) age at onset was 71.1±7.0 years (range, 50 to 59), and 63 percent of the subjects were women.
‡ In the patient–control data set, the mean age at onset was 70.8±6.6 years (range, 51 to 87), and 67 percent of the subjects were women.
§ The Family-Based Association Test is described by Bertram et al.,[1] the Pedigree Disequilibrium Test by Martin et al.,[4] and the Quantitative Transmission Disequilibrium Test by Abecasis et al.[5]

4. Martin ER, Bass MP, Gilbert JR, Pericak-Vance MA, Hauser ER. Genotype-based association test for general pedigrees: the genotype-PDT. Genet Epidemiol 2003;25:203-13.
5. Abecasis GR, Cardon LR, Cookson WO. A general test of association for quantitative traits in nuclear families. Am J Hum Genet 2000;66:279-92.

THE AUTHORS REPLY: We are pleased by Slifer and colleagues' report of a significant genetic association between single-nucleotide polymorphisms in the *UBQLN1* gene and the age at onset of Alzheimer's disease in two separate and independent samples, providing further support for our original finding that *UBQLN1* variants may influence the pathogenesis of Alzheimer's disease.[1] Given the significant age-at-onset effects in their samples, it is puzzling that they did not observe significant effects on the risk of disease, since these two traits are correlated. Possible explanations include allelic heterogeneity, lack of power in the risk analyses, and methodologic differences in sample ascertainment and statistical procedures.

It is also worth noting that the two original linkage signals (according to a binary phenotype definition) reported for the family-based sample analyzed by Slifer et al.[2] were located more than 40 cM away (in either direction) from *UBQLN1* and our linkage peak.[3] Thus, their sample may not be optimal for detecting risk effects of the magnitude described in our initial report.[3] Notwithstanding these differences, the fact that several *UBQLN1* single-nucleotide polymorphisms now show an association with either the age at onset or the risk of Alzheimer's disease in a number of independent samples suggests the possibility of linkage disequilibrium with one or more additional pathogenic variants.

Along these lines, since our original report,[1] we have now found additional evidence of an association between the risk of Alzheimer's disease and the T allele of a *UBQLN1* promoter single-nucleotide polymorphism (rs12345514) in both the National Institutes of Mental Health family sample (P=0.02 by the Family-Based Association Test) and the Consortium on Alzheimer's Genetics family sample (P=0.04). The combined data sets yielded the strongest evidence of an association (P=0.002), which is consistent with our previous findings. Collectively, these data suggest that the pathogenesis of Alzheimer's disease may be influenced by changes not only in the splicing of *UBQLN1*,[1] but also in its expression. Ultimately, meta-analysis of these and additional association studies[4] should provide a more precise measure of the actual contribution of *UBQLN1* variants to Alzheimer's disease.

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3. Blacker D, Bertram L, Saunders AJ, et al. Results of a high-resolution genome screen of 437 Alzheimer's disease families. Hum Mol Genet 2003;12:23-32.
4. Alzheimer Research Forum. The AlzGene database. (Accessed June 9, 2005, at http://www.alzgene.org.)