# *APOE ϵ4* is associated with obstructive sleep apnea/hypopnea

## The Sleep Heart Health Study

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**Abstract—***Background:* Obstructive sleep apnea/hypopnea (OSAH) has a strong heritable component, although its genetic basis remains largely unknown. One epidemiologic study found a significant association between the *APOE ϵ4* allele and OSAH in middle-aged adults, a finding that was not replicated in a cohort of elderly adults. The objective of this study was to further examine the association of the *APOE ϵ4* allele with OSAH in a community-dwelling cohort, exploring age dependency of the association. *Methods:* A genetic association study was performed, nested within a prospective cohort study of the cardiovascular consequences of OSAH. Unattended, in-home nocturnal polysomnography was used to measure apnea-hypopnea index (AHI) in 1,775 participants age 40 to 100 years. OSAH was defined as an AHI ≥ 15. The relation of *APOE* genotype to prevalent OSAH was analyzed using generalized estimating equations to account for non-independent observations of individuals from the same sibship. *Results:* At least one *APOE ϵ4* allele was present in 25% of subjects, with 1.3% ϵ4/ϵ4 homozygotes. The prevalence of OSAH was 19%. After adjustment for age, sex, and BMI, the presence of any *APOE ϵ4* allele was associated with increased odds of OSAH (OR 1.41, 95% CI 1.06 to 1.87, $p = 0.02$). The effect was approximately twice as great in subjects <75 (OR 1.61, CI 1.02 to 2.54) as in those ≥75 years old (OR 1.32, CI 0.91 to 1.90). Exploratory analyses revealed that the strongest effect of *APOE ϵ4* was in subjects age <65 (OR 3.08, CI 1.43 to 6.64), and was stronger in those with hypertension or cardiovascular disease than in those without. *Conclusion:* The *APOE ϵ4* allele is associated with increased risk of OSAH, particularly in individuals under age 65. The mechanisms underlying this association are uncertain. Age-dependency of the *APOE*-OSAH association may explain previous conflicting results.

NEUROLOGY 2004;63:664–668

Obstructive sleep apnea/hypopnea (OSAH), characterized by repetitive episodes of partial or complete upper airway closure during sleep, is a common adult disorder. OSAH associated with excessive daytime sleepiness is estimated to affect at least 2% of middle-aged women and 4% of middle-aged men in the United States, although the prevalence of OSAH independent of daytime symptoms is much higher, affecting 9 to 24% of middle-aged US adults[1] and an even higher proportion of elderly adults.[2] Obesity is an important risk factor for OSAH, although there is evidence that OSAH has a strong heritable component independent of body habitus.[3,4] The genetic basis of this heritability remains largely unknown. In light of the known association between cardiovascular disease (CVD) and both OSAH and *APOE* genotype, several studies have explored the relation of *APOE* genotype to OSAH, with conflicting results. Among the middle-aged adult participants in the Wisconsin Sleep Cohort Study (WSCS), the presence of an *APOE ϵ4* allele was associated with a twofold increased odds of OSAH,[5] although no such association was observed among the elderly participants in the Honolulu-Asia Aging Study (HAAS)[6] or in a group of Finnish OSAH patients compared with healthy controls.[7] Recently, a genome-wide linkage study in the Cleveland Family Study found suggestive evidence of linkage to AHI in a region of chromosome 19 that includes the *APOE* gene.[8] In this study, we further explored the association of *APOE* genotype with OSAH, looking for possible modification of this association by age, hypertension, and prevalent CVD, in a sample of 1,775 participants in the Sleep Heart Health Study (SHHS).

**Methods.** The SHHS is a longitudinal cohort study of the relation of sleep-disordered breathing to CVD, whose 6,441 participants were recruited from several on-going epidemiologic studies of CVD and underwent overnight polysomnography, as previously described.[9] The parent studies include the Framingham Heart Study (FHS) and Cardiovascular Health Study (CHS), which had

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Supported by National Heart, Lung and Blood Institute cooperative agreements U01 HL53940 (University of Washington), U01 HL53941 (Boston University), U01 HL53938 (University of Arizona), U01 HL53916 (University of California, Davis), U01 HL53934 (University of Minnesota), U01 HL53931 (New York University), U01 HL53937 and U01 HL64360 (Johns Hopkins University), U01 HL63463 (Case Western Reserve University), and U01 HL63429 (Missouri Breaks Research), and research grant R01 HL71515 (Stanford University).

Received November 14, 2003. Accepted in final form April 26, 2004.

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previously genotyped *APOE* in their participants and contributed genotype data for this analysis. Of the 700 FHS participants and 1,250 CHS participants who participated in the SHHS, *APOE* genotype was available for 1,778 subjects (91%). Three of these subjects were excluded due to missing data on body mass index (BMI) from the time of polysomnography. The remaining 1,775 subjects are included in this analysis. Among the FHS subjects are 123 with blood relatives included in the analysis (45 pedigrees with two siblings, 7 with three siblings, and 3 with four siblings).

Overnight polysomnography was performed in subjects' homes with the Compumedics Portable PS-2 System (Abottsville, AU) using methods previously detailed.[10,11] Briefly, sensors were placed and equipment was calibrated during an evening visit by a certified technician. Data collection included EEG, electrooculography, submental EMG, thoracic and abdominal excursions by inductive plethysmography, nasal-oral thermistry, finger pulse oximetry, and EKG. Manual scoring of sleep and respiratory signals was performed at a central Reading Center. Sleep stages were scored according to the guidelines developed by Rechtschaffen and Kales,[12] and arousals scored according to the American Sleep Disorders Association Atlas Task Force definition.[13] Apnea was defined as a complete or almost complete cessation of airflow (<25% of baseline), as measured by the amplitude of the thermocouple signal, lasting > 10 seconds. Hypopnea was identified if the amplitude of the thermocouple or thoracic or abdominal inductance band signal decreased to < 70% of the baseline amplitude for > 10 seconds, but did not meet the criteria for apnea. Only apneas or hypopneas associated with at least a 4% oxyhemoglobin desaturation were considered in the calculation of the apnea-hypopnea index (AHI), defined as the number of apneas plus hypopneas during sleep divided by total sleep time. *APOE* genotype was determined in each parent cohort, under Institutional Review Board-approved informed consent specific for genetic testing, using gene amplification and restriction isotyping as previously described.[14,15] Fasting serum total and HDL cholesterol concentration, BMI, and waist circumference were provided by the parent cohorts from the study clinic visit most nearly preceding the polysomnogram. On the evening of the polysomnogram, blood pressure and neck circumference were measured, medication use was recorded, and self-report of doctor-diagnosed angina, myocardial infarction, stroke, or congestive heart failure was obtained.

For these analyses, the presence of OSAH was defined as AHI ≥ 15. The relation of *APOE* genotype to OSAH was examined using generalized estimating equations in order to account for non-independence of observations from siblings, using PROC GENMOD in SAS (SAS 8.0, SAS Institute, Cary, NC). Because of their known impact on AHI, all models included adjustment for sex and for age and BMI as continuous variables. Results are presented as adjusted OR with 95% CI. The primary analysis included the entire study sample, with a planned secondary analysis stratified at age 75, approximately the median age in our sample and an age between the oldest subjects in the WSCS[5] and the youngest in the HAAS[6] reports. Exploratory analyses stratified on age, using thresholds at 5-year intervals from 60 to 80, assessed the age of peak *APOE* effect. Analyses including an indicator variable for parent cohort (FHS vs CHS), or stratified on parent cohort, were also performed to assess heterogeneity across cohorts. Additional analyses adjusted for serum total and high density lipoprotein (HDL) cholesterol concentration, in order to assess whether the effects of *APOE* were mediated through effects on serum lipids, and for race and the presence of hypertension or CVD as possible confounders of the *APOE*-OSAH association. Exploratory analyses stratified by the presence or absence of hypertension or CVD were performed to evaluate possible effect modification by the presence of these conditions.

**Results.** The mean age of the 1,775 subjects was 71 years (SD 10.5, range 40 to 100) and 55% were women. Eighty-eight percent of subjects were non-Hispanic white, 12% non-Hispanic black, and less than 1% of other race/ethnicity. The *APOE ϵ4* allele frequency was 13.0% (12.0% in subjects < 75 years old, 14.0% in subjects ≥75 years old). At least one *APOE ϵ4* allele was present in 25% of subjects, with only 1.3% ϵ4/ϵ4 homozygotes. The distribution of *APOE* genotypes did not differ significantly from Hardy-Weinberg equilibrium. Due to the small number of

***Table 1*** *Participant characteristics by APOE ϵ4 genotype*

| Characteristics | *APOE ϵ4*-negative, n = 1,336 | *APOE ϵ4*-positive, n = 439 | *p* Value* |
|---|---|---|---|
| Age, y | 71.4 ± 10.7 | 72.1 ± 9.9 | 0.22 |
| Women, % | 54.8 | 55.4 | 0.84 |
| White, % | 88.7 | 85.4 | 0.07 |
| BMI, kg/m$^2$ | 27.9 ± 4.8 | 27.3 ± 4.6 | 0.01 |
| Neck circumference, cm | 37.6 ± 4.0 | 37.1 ± 3.6 | 0.02 |
| Waist circumference, cm | 96.6 ± 13.7 | 95.7 ± 12.8 | 0.21 |
| Total cholesterol, mg/dL | 202.7 ± 37.6 | 208.0 ± 37.0 | 0.01 |
| HDL cholesterol, mg/dL | 52.6 ± 14.8 | 50.6 ± 14.0 | 0.02 |
| Triglycerides, mg/dL | 146.0 ± 93.0 | 142.6 ± 14.6 | 0.48 |
| Hypertension, % | 55.6 | 58.6 | 0.27 |
| Coronary artery disease, % | 17.1 | 19.2 | 0.31 |
| Stroke, % | 5.2 | 7.4 | 0.09 |
| Congestive heart failure, % | 3.3 | 2.8 | 0.57 |
| Current smokers, % | 7.9 | 8.5 | 0.14 |
| Smoking, pack-years | 14.7 ± 23.3 | 16.8 ± 25.1 | 0.13 |
| $FEV_1$, L | 2.30 ± 0.79 | 2.24 ± 0.78 | 0.14 |

Values are mean ± SD or %.

* Based on $\chi^2$ test for comparing percents and *t*-test for comparing means, with correction for unequal variances when appropriate.

BMI = body mass index; HDL = high-density lipoprotein.

***Table 2*** *Association of APOE ϵ4 allele with obstructive sleep apnea/hypopnea (OSAH)*

| Group | N | OR for OSAH*, ϵ4+ vs ϵ4− subjects | 95% CI | *p* Value |
|---|---|---|---|---|
| Total sample | 1,775 | 1.41 | 1.06–1.87 | 0.02 |
| Age group, y | | | | |
| <75 | 870 | 1.61 | 1.02–2.54 | 0.04 |
| ≥75 | 905 | 1.32 | 0.91–1.90 | 0.14 |
| <65 | 398 | 3.08 | 1.43–6.64 | 0.004 |
| ≥65 | 1,377 | 1.25 | 0.93–1.69 | 0.15 |
| Presence of hypertension† | | | | |
| Hypertension absent | 770 | 1.25 | 0.78–2.00 | 0.35 |
| Hypertension present | 994 | 1.47 | 1.03–2.10 | 0.03 |
| Presence of cardiovascular disease‡ | | | | |
| CVD absent | 1,376 | 1.24 | 0.88–1.74 | 0.22 |
| CVD present | 394 | 1.89 | 1.13–3.17 | 0.02 |

* Adjusted in total sample and within each stratum for age, sex, and body mass index. Generalized estimating equations used to account for non-independent observations of individuals from the same sibship.

† Hypertension defined as systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg, or taking antihypertensive medication.

‡ Cardiovascular disease (CVD) is defined as the self-report of doctor diagnosed angina, myocardial infarction, stroke, or congestive heart failure.

*APOE ϵ4* homozygotes, the primary analyses compared subjects with any *APOE ϵ4* allele to those without. As expected, the presence of the *APOE ϵ4* allele was associated with a significantly higher total cholesterol and lower HDL cholesterol, despite slightly less adiposity (table 1). *APOE ϵ4*-positive subjects did not differ significantly from ϵ4-negative subjects in smoking history or mean $FEV_1$. *APOE ϵ4* positivity was associated with a somewhat higher prevalence of coronary heart disease, stroke, and hypertension, although these differences were not significant.

The median AHI across all study subjects was 4.8 (range 0 to 149, interquartile range 1.6 to 11.9); 19.0% had OSAH, defined as an AHI ≥ 15, including 241 (18.0%) of 1,336 subjects without and 97 (22.1%) of 439 with an *APOE ϵ4* allele. After adjustment for age, sex, and BMI, the presence of any *APOE ϵ4* allele was associated with a 41% increased odds of OSAH (adjusted OR 1.41, CI 1.06 to 1.87; table 2). Adjustment for race had no impact on the estimated effect of *APOE ϵ4* on OSAH, but there were too few non-white subjects to make meaningful comparisons across races. Neither total nor HDL cholesterol was significantly associated with the presence of OSAH, and adjustment for these variables did not appreciably alter the association of *APOE ϵ4* with OSAH (age-, sex-, and BMI-adjusted OR 1.45 with total cholesterol in model, 1.47 with HDL cholesterol in model). The association of *APOE ϵ4* with OSAH was similar in men and women, with an age- and BMI-adjusted OR of 1.46 in men and 1.42 in women. The association of *APOE ϵ4* with OSAH was also similar in non-obese (BMI < 30, n = 1,289) and obese (BMI ≥ 30, n = 486) subjects, with age- and sex-adjusted OR of 1.34 in non-obese and 1.47 in obese subjects. The 24 subjects homozygous for *APOE ϵ4* did not have increased odds of OSAH compared to subjects with no ϵ4 allele (age, sex, and BMI-adjusted OR 0.86, CI 0.26 to 2.89), although the small number of subjects makes the effect estimate unreliable.

At least one *APOE ϵ2* allele was present in 15.6% of subjects. Inclusion in the models of a variable reflecting the presence or absence of an *APOE ϵ2* allele had no meaningful impact on the association of *APOE ϵ4* with OSAH (age-, sex-, BMI-, and ϵ2-adjusted OR 1.38, CI 1.04 to 1.83). The presence of an *APOE ϵ2* allele was in the direction of reduced risk for OSAH but was not significant (age-, sex-, BMI-, and ϵ4-adjusted OR 0.80, CI 0.55 to 1.15).

The association of the *APOE ϵ4* allele with OSAH was approximately twice as great in subjects <75 than in those ≥75 years old (see table 2). Although age 75 was chosen a priori for age stratified analyses, exploratory analysis of age thresholds at 5-year intervals was undertaken to further explore age dependency of the association of *APOE* to OSAH. The age of peak effect was approximately 65 years. Among subjects age <65, the age, sex, and BMI-adjusted OR was 3.08 (CI 1.43 to 6.64), vs an adjusted OR of 1.25 in subjects age ≥65 (CI 0.93 to 1.69). Despite these differences in estimated effect, formal tests of interaction of age group by *APOE* genotype were not significant for either age 75 ($p = 0.56$) or age 65 ($p = 0.10$). The age of subjects enrolled in the SHHS from the CHS cohort are considerably older (mean [SD] age 77.6 [4.8] years) than those enrolled from the FHS cohort (59.8 [8.9] years), and all subjects age <65 years are from the FHS cohort. We therefore evaluated whether cohort effects other than age might account for the apparent age-dependency of the *APOE*-OSAH association. Inclusion of an indicator variable for parent cohort (FHS vs CHS) had no impact on the magnitude of the *APOE*-OSAH association. When the analysis was stratified by parent cohort, the age, sex, and BMI-adjusted OR in the FHS sample (2.27 [CI 1.28 to 4.02]) was higher than that in the CHS sample (1.20 [CI 0.87 to 1.66]). However, this is due primarily to a higher OR in FHS subjects under age 65 (3.08 [CI 1.43 to 6.64]), as the OR in FHS subjects age ≥65 was similar to that in the CHS cohort (1.69 [CI 0.73 to 3.91]).

Using a threshold of AHI ≥ 30 to define OSAH, the

prevalence of OSAH in the study sample was 6.4%. The association of *APOE ϵ4* allele with OSAH defined in this way was similar to the association observed when OSAH was defined as AHI ≥ 15, and the apparent age-dependency of the association was even more striking. For the entire sample, the age-, sex-, and BMI-adjusted OR was 1.46 (CI 0.95 to 2.23). In subjects age <75 the adjusted OR was 2.49 (CI 1.24 to 5.02), while in those age ≥75 the adjusted OR was 1.04 (CI 0.59 to 1.83).

Stratification of the sample by the presence or absence of hypertension, defined as systolic blood pressure > 140, diastolic blood pressure > 90, or taking antihypertensive medication, revealed that the age-, sex-, and BMI-adjusted association of *APOE ϵ4* with OSAH was seen primarily in hypertensive subjects (see table 2). When this analysis was further stratified by age above or below 75, the association of *APOE ϵ4* with OSAH was stronger in the hypertensive subjects age <75. The magnitude of the association of *APOE ϵ4* with OSAH was also greater in subjects reporting prevalent CVD than in those free of CVD (see table 2), and this effect was also stronger in younger subjects. Inclusion of prevalent hypertension and CVD as covariates in the main analysis did not, however, diminish the strength of the association of *APOE ϵ4* with OSAH.

Periodic breathing, defined as cyclic waxing and waning of thermocouple or inductance band signals lasting for at least 10 minutes, was present in 5% of subjects. The *APOE ϵ4* allele was not associated with periodic breathing, with an age-, sex-, and BMI-adjusted OR of 0.94 (CI 0.57 to 1.55). In order to assess whether sleep state instability might mediate the *APOE*-OSAH association, we analyzed the relation of *APOE* genotype to arousal index. Overall, 24% of subjects had an arousal index ≥ 25. Despite a moderate correlation between AHI and arousal index (r = 0.49), there was no significant association between the presence of the *APOE ϵ4* allele and elevated arousal index in either unadjusted or age-, sex-, and BMI-adjusted models, with the direction of effect toward a lower arousal index in those with the *APOE ϵ4* allele.

**Discussion.** These findings support the previously reported association between the *APOE ϵ4* allele and OSAH observed in the WSCS.[5] The magnitude of the *APOE ϵ4*-OSAH association was similar in men and women, and in obese and non-obese subjects, but declined with advancing age. The strongest *APOE ϵ4*-OSAH association was seen in individuals under age 65; however, there were too few subjects under age 60 to determine the pattern of age dependency at younger ages. A similar age dependency has been reported for the association of *APOE ϵ4* with coronary atherosclerosis[16] and Alzheimer disease (AD).[17] The FHS cohort is considerably younger than the CHS cohort, suggesting the possibility that cohort effects other than age might lead to an apparent age-dependency of the *APOE*-OSAH effect; however, magnitude of the *APOE*-OSAH association is considerably greater in FHS subjects <65 years old than in those ≥65. This suggests that the age effect observed for the entire study sample is not likely to reflect confounding by cohort differences other than age. Given the substantially higher mean AHI in older subjects, it is likely that this age dependency reflects competing risk factors for OSAH in the elderly. As the *APOE ϵ4* allele frequency was somewhat higher in older than in younger subjects (14.0% vs 12.0%), it is unlikely that age-dependency of the *APOE*-OSAH association is due to excess death or other loss to follow-up among *APOE ϵ4*-positive subjects with OSAH. In either case, the disagreement between prior epidemiologic studies of the *APOE*-OSAH association[5,6] may be explained by age-dependency of the association.

Our sample had insufficient minority representation to explore effect modification by race, and included few subjects of Asian ancestry. The prevalence of *APOE ϵ4* positivity in our sample (25%) was similar to that in the WSCS (28%), but somewhat higher than that in the HAAS (18%). The lower prevalence in that cohort may reflect the known lower prevalence of the *APOE ϵ4* allele in Japanese.[17] In the study of Finnish OSAH patients and controls, the prevalence of *APOE ϵ4* positivity was 34%.[7] While a similar association of *APOE ϵ4* to OSAH would be expected across races if the *APOE ϵ4* allele were a functional polymorphism causing OSAH, heterogeneity of the effect of *APOE* genotype across different genetic backgrounds (predominantly northern European in WSCS vs Japanese in HAAS) cannot be excluded. As is the case for AD, the *APOE ϵ2* allele was associated with reduced odds of OSAH, although this effect was not significant.

In exploratory analyses, the present study finds evidence of a possible interaction of *APOE ϵ4* and hypertension in causing OSAH. This is consistent with evidence that hypertension may act synergistically with *APOE ϵ4* to increase risk of cognitive impairment[18] and that treatment of hypertension may decrease the risk of AD.[19] The greater risk of OSAH in *APOE ϵ4*-positive subjects with prevalent CVD might also reflect an interaction of *APOE ϵ4* with other cardiovascular risk factors in mediating the pathophysiologic processes resulting in OSAH, but raises the intriguing possibility that *APOE* genotype may modify the cardiovascular risk of OSAH. While these findings suggest effect modification by hypertension or CVD, there is no evidence from this study for confounding of the *APOE*-OSAH association by these factors.

The mechanism of the effect of *APOE* genotype on OSAH is unknown, although the potential importance of a causal association would be substantial. As at least one *APOE ϵ4* allele is present in approximately 25% of the population, the observed OR and their 95% CI suggest that 9% (CI 1.5 to 18%) of all OSAH cases in the adult population and 34% (CI 10 to 58%) of OSAH cases in adults under age 65 may be attributable to the *APOE ϵ4* genotype. OSAH is most often the result of an anatomically small or collapsible pharyngeal airway, often due to obesity, in combination with a sleep-induced fall in pharyngeal dilator muscle activity.[20] It does not appear that *APOE ϵ4* genotype has an adverse impact on adipos-

ity, as *APOE ϵ4*-positive subjects were less obese whether assessed by BMI, waist girth, or neck circumference. Unless *APOE* has an obesity-independent effect on upper airway anatomy, it is likely that its effect is mediated through alterations in ventilatory control mechanisms. The lack of association between *APOE* genotype and elevated arousal index suggests that sleep state instability probably does not mediate such an effect. Although pure central sleep apnea is uncommon in younger subjects, and we did not observe an association of *APOE ϵ4* with classic periodic breathing, cyclic decreases in output from respiratory motoneurons innervating upper airway dilator muscles has been demonstrated in obstructive as well as central sleep apnea.[21,22] Thus, central mechanisms may result in obstructive apnea or hypopnea in anatomically susceptible individuals.

As expected, the *APOE ϵ4* allele was associated with significantly higher total cholesterol and lower HDL cholesterol. Higher cholesterol level has been shown to predict development of OSAH,[23] and in the SHHS cohort AHI has a significant positive correlation with total cholesterol in men, and a significant negative correlation with HDL cholesterol in women.[24] While it would be attractive to attribute the *APOE*-OSAH association to cholesterol-related mechanisms, the magnitude of the association is not diminished by inclusion of total or HDL cholesterol in the regression models. Therefore, by the standard assumptions of mediation analysis,[25] the effect of *APOE* on OSAH is not likely to be mediated through the well-known effects of *APOE* on serum cholesterol concentration. It is possible that *APOE ϵ4* exerts its effect as part of the neuropathologic processes that are implicated in the development of *APOE ϵ4*-related AD. Despite the earlier age at onset of OSAH, some pathologic changes associated with AD can be observed even in asymptomatic carriers of the *APOE ϵ4* allele.[26] While the pathogenesis of *APOE ϵ4*-related AD is complex, and its relevance to OSAH remains speculative, degeneration of brainstem respiratory centers with consequent decreased activity of respiratory motoneurons innervating the pharyngeal dilator muscles is a plausible mechanism underlying the *APOE*-OSAH association. An analogous process in patients with multiple system atrophy has been suggested by the finding that the severity of OSAH in these patients is highly correlated with loss of cholinergic projections from the pedunculopontine tegmental and laterodorsal tegmental nuclei.[27] Alternatively, given its role in lipid metabolism, *APOE* might influence ventilatory drive through effects on leptin or other adipokines, although such effects remain to be demonstrated.


### Acknowledgment

Sleep Heart Health Study (SHHS) acknowledges the Atherosclerosis Risk in Communities Study (ARIC), the Cardiovascular Health Study (CHS), the Framingham Heart Study (FHS), the Cornell/Mt. Sinai Worksite and Hypertension Studies, the Strong Heart Study (SHS), the Tucson Epidemiologic Study of Airways Obstructive Diseases (TES), and the Tucson Health and Environment Study (H-E) for allowing their cohort members to be part of the SHHS and for permitting data acquired by them to be used in the study. SHHS also thanks the members of these cohorts who agreed to participate in SHHS. SHHS further recognizes all of the investigators and staff who have contributed to its success. A list of SHHS investigators, staff, and their participating institutions is available on the SHHS Web site: www.jhsph.edu/shhs


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