ORIGINAL REPORT

Sleep Apnea Symptoms and Risk of Temporomandibular Disorder: OPPERA Cohort

A.E. Sanders[1]*, G.K. Essick[1], R. Fillingim[2], C. Knott[3], R. Ohrbach[4], J.D. Greenspan[5], L. Diatchenko[1], W. Maixner[1], R. Dubner[5], E. Bair[1], V.E. Miller[6], and G.D. Slade[7]

APPENDIX

Follow-up in the OPPERA Prospective Cohort Study

The inception cohort consisted of 3,263 participants who did not have temporomandibular disorder (TMD), although post-enrollment audits found that five were ineligible, and they were excluded from all analysis. Sixteen percent (521/3,258) of the 3,258 eligible enrollees completed no follow-up questionnaires, 35% (1,154/3,258) participants completed all intended quarterly health updates through May 2011 (and hence were administratively censored), while the remaining 49% (1,583/3,258) completed fewer follow-up questionnaires than intended. The 26,666 follow-up questionnaires represented a median of 10 quarterly health updates *per* person, somewhat less than the median of 14 questionnaires *per* person that would have been completed had there been no partial loss to follow-up prior to May 2011. The shortfall between the number of intended questionnaires through May 2011 and the number completed represented the degree of partial loss to follow-up. The median shortfall was 3 questionnaires *per* person, with lower and upper quartiles of 0 and 9 questionnaires, respectively. The median period of follow-up was 2.8 yrs *per* person (minimum = 0.2 yrs, maximum = 5.2 yrs), for a total of 7,403 person-years of follow-up.

Evaluation of Potential Bias Associated with Loss to Follow-up

This section summarizes findings from analysis of loss to follow-up in the OPPERA prospective cohort study [Bair E, Brownstein NC, Ohrbach R, Greenspan JD, Dubner R, Fillingim RB, *et al*. Study design, methods, sample characteristics and loss to follow-up: the OPPERA prospective cohort study. *J Pain* (submitted Feb. 6, 2013)].

The percentage of participants retained in the cohort varied significantly according to gender, race, and study site, although not age (Appendix Table 1). As reported in Bair *et al*. (see above), loss to follow-up was also analyzed according to 157 other putative risk factors measured at enrollment. At least 5 measures within each of the 4 risk factor domains were associated with complete loss to follow-up to a degree that exceeded chance, as judged by quantile-quantile plots.

'Hot deck' multiple imputation was used to evaluate potential bias due to loss to follow-up [Andridge RR, Little RJ (2010). A review of hot deck imputation for survey non-response. *Int Stat Rev* 78:40-64. PMID 21743766]. The method creates groups composed of people with similar baseline characteristics ("hot decks"), within which observed outcomes from people with follow-up data were used to impute likely outcome values for people with no follow-up data. There were five steps:

(1) Eight baseline predictor variables were selected because they were associated with both loss to follow-up and TMD incidence: study site, age, gender, number of body sites that were tender to palpation, changes in mean arterial blood pressure during the Stroop emotional word task, pressure pain thresholds measured at the trapezius, and the Perceived Stress Scale. They were used in a multivariable binary logistic model regression to predict odds of complete loss to follow-up for all participants in the inception cohort.

(2) Participants in the inception cohort were ranked according to the value of the model's linear predictor, from which 20 equal-sized strata were calculated, each with a successively greater probability of complete loss to follow-up.

(3) For each of the 521 participants completely lost to follow-up, one participant was sampled at random from

DOI: 10.1177/0022034513488140. [1]University of North Carolina at Chapel Hill, Koury Oral Health Sciences Building, 385 South Columbia Street, Chapel Hill, NC 27599-7450, USA; [2]University of Florida College of Dentistry; [3]Battelle Memorial Institute, Durham, NC, USA; [4]Department of Oral Diagnostic Sciences, University of Buffalo, USA; [5]University of Maryland, Baltimore, MD, USA; [6]School of Global Public Health, University of North Carolina at Chapel Hill, Gillings, Chapel Hill, NC, USA; and [7]University of North Carolina, Chapel Hill, NC, USA; *corresponding author, anne_sanders@dentistry.unc.edu

Appendix Table 1.

Associations between Risk for Obstructive Sleep Apnea (OSA) and Site-adjusted and Fully Adjusted Associations of Baseline Resting (reclined) Autonomic Measures [mean (standard error)][a], OPPERA Prospective Cohort, 2006-2008

Autonomic Variable	Mean Arterial Pressure (MAP), mm Hg		Mean Heart Rate (HR) Beats *per* Min (bpm)		HR/MAP[a] bpm/mm Hg		SDNN[b] Mean squared (ms)		RMSSD[c] ms		Log LF[d]	
Summary measure: Likelihood of OSA [e]	**Site-adjusted**	**Fully Adjusted[f]**	**Site-adjusted**	**Fully Adjusted[f]**	**Site-adjusted**	**Fully Adjusted[f]**	**Site-adjusted**	**Fully Adjusted[f]**	**Site-adjusted**	**Fully Adjusted[f]**	**Site-adjusted**	**Fully Adjusted[f]**
Low likelihood	82.59 (0.17)	83.13 (0.31)	62.91 (0.21)	63.83 (0.40)	0.77 (0.00)	0.77 (0.01)	79.02 (0.82)	75.32 (1.57)	74.39 (1.34)	67.55 (2.58)	5.87 (0.02)	5.80 (0.04)
High likelihood	86.55 (0.66)	84.29 (0.66)	65.32 (0.81)	65.12 (0.86)	0.76 (0.01)	0.78 (0.01)	72.10 (3.18)	75.34 (3.37)	72.14 (5.20)	74.61 (5.57)	5.73 (0.08)	5.79 (0.09)
***p* value**	< .001	.069	.004	.120	.605	.619	.036	.994	.675	.191	.090	.924

(a) HR/MAP is a measure of the relative balance of cardiosympathetic *vs.* cardioparasympathetic tone at a given baroreflex set point (MAP). Higher values reflect greater sympathetic *vs.* parasympathetic tone and diminished baroreflex sensitivity.

(b) SDNN refers to the autonomic standard deviation of normal-to-normal [N-N] intervals. The normal-to-normal interval length is the interval from the peak of one QRS complex to the peak of the next.

(c) RMSSD refers to the autonomic root mean square of the differences between successive N-N intervals.

(d) Log LF low-frequency band of the power spectrum, which reflects both sympathetic and parasympathetic activity. During slow regular breathing (resting state), it is dominated by parasympathetic activity. Higher values are associated with greater baroreflex sensitivity.

(e) High likelihood of OSA is a summary variable derived from ≥ 2 affirmative responses to four questions that approximate items in the STOP screening questionnaire for OSA or a self-reported history of sleep apnea.

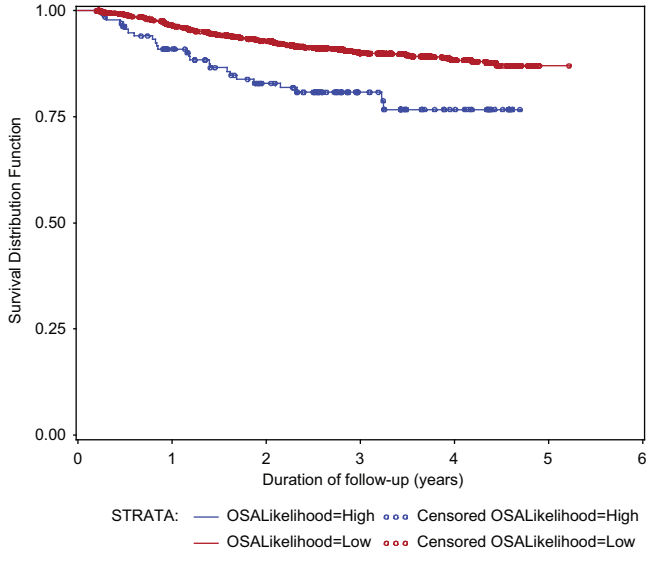
(f) Estimates are additionally adjusted for gender, age, race/ethnicity, BMI, and smoking.

Appendix Table 2.
Loss to Follow-up, OPPERA Prospective Cohort Study, 2006-2011

		% of People in Follow-up Category[a]			
	n	Complete	Partial	None	*p* value[b]
All people	3,258	35.4	48.6	16.0	
Age when enrolled (yrs)					
18-24	1,706	33.5	49.8	16.7	.097
25-34	860	39.0	46.6	14.4	
35-44	692	35.7	48.1	16.2	
Gender					
Female	1,862	40.9	46.7	12.5	< .001
Male	1,396	28.2	51.2	20.7	
Race/ethnicity					
White	1,637	43.4	45.1	11.6	< .001
Black/African-American	1,012	21.9	53.8	24.3	
Asian	299	40.1	45.5	14.4	
Hispanic	211	34.1	50.2	15.6	
Other or unstated	99	30.3	59.6	10.1	

[a]Complete = All quarterly follow-up questionnaires completed. Partial = Some quarterly follow-up questionnaires completed. None = No quarterly follow-up questionnaires completed.
[b]*p* value from Chi-square test of null hypothesis that distribution of follow-up categories is equivalent between demographic groups.

Appendix Figure.
TMD-free survival in people with low and high likelihood of obstructive sleep apnea (OSA): OPPERA prospective cohort study 2006-2011 (n = 2,604).



among all participants in the same stratum who provided follow-up data. The method used simple random sampling with replacement. The sampled participant's follow-up status (first-onset TMD or censored) and period of follow-up were used as the imputed estimates for the individual lost to follow-up.

(4) The imputed records were added to the records from 2,737 participants who had follow-up data, creating a dataset of 3,258 individuals with complete information about TMD incidence and follow-up period.

(5) Steps 3 and 4 were repeated 100 times, with independent random sampling in each replication. Incidence rates and hazard ratios were calculated for each of the 100 replicated datasets. The 100 sets of results were combined by the "mianalyze" procedure in SAS to generate valid estimates of rates, rate ratios, and standard errors.

The imputed annual incidence rate of 3.5% *per annum* was identical to the observed rate computed in complete-case analysis (Appendix Table 2). Baseline predictors of TMD incidence in the complete-case analysis were likewise associated with the imputed incidence rate, while gender was not. Compared with the complete-case analysis, hazard ratios differed by no more than 0.1 in absolute value.