Predictors of Longitudinal Change in Sleep-Disordered Breathing in a Nonclinic Population

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Study Objectives: To quantify and identify the determinants of the 5-year change in the respiratory disturbance index (RDI).
Design: Longitudinal cohort study (Cleveland Family Study). Multivariate analyses were used to quantify baseline RDI and RDI change.
Setting: Community-based study.
Participants: 486 cohort members (62% from families of probands with sleep-disordered breathing [SDB])—mean age 31.6 ± 17.9 (SD) years, 60% female, 21% Black ethnicity—who underwent 2 assessments over 5.3 ± 0.9 (SD) years.
Interventions: NA
Measurements: The RDI was measured twice over approximately 5 years with in-home monitoring. Symptoms and medical histories were obtained from standardized questionnaires, and weight, height, and blood pressure were measured.
Results: The prevalence of SDB (defined by a RDI ≥ 15), increased from 13.7% to 23.4% (P<0.01) in men and from 8.3% to 11.4% (P=0.13) in females. Baseline and follow-up mean RDIs were 6.0±10.0 and 8.6±14.3; both were higher in older individuals, in men, and in those with a higher body mass index. Median 5-year change in RDI varied nonlinearly with age (-0.1, 1.1, 2.3, and 0.9, for those <18, 19-40, 41-54, and ≥ 55 years, respectively) and obesity (2.8 vs –0.1, for the top versus lowest body mass index quartile). The effects of changing weight and aging varied in population subgroups. At any given age and weight, the RDI increased less in women.
Conclusions: Longitudinal change in the RDI varies nonuniformly with age, sex, and weight. Older heavier men may experience the highest rate of increase in RDI over time and, thus, may benefit most from prospective monitoring.
Key Words: sleep apnea; epidemiology; longitudinal study
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INTRODUCTION

SLEEP-DISORDERED BREATHING (SDB), A DISORDER CONSISTING OF REPETITIVE EPISODES OF INTERMITTENT PHARYNGEAL OBSTRUCTION DURING SLEEP WITH CONSEQUENT ARTERIAL OXYGEN DESATURATION, SLEEP FRAGMENTATION, SNORING, AND SLEEPINESS, AFFECTS AT LEAST 9% TO 15% OF MIDDLE-AGED ADULTS.[1] Prevalence may be higher in other segments of the population such as the elderly and African American children.[2,3] The association of SDB with obesity, hypertension (HTN), diabetes, and cardiovascular disease (CVD)[4-8] has highlighted the broad public health importance of this condition. Cross-sectional data from the Sleep Heart Health Study, a large prospective study of SDB,[9] indicate that even modest levels of SDB increase the risk of HTN by 40% to 70%[10] and of CVD by 30% to 40%.[11]

The public health importance of SDB underscores the need to understand the natural history of SDB and its association with host and environmental risk factors. This may be useful for population screening and case finding and for clarifying mechanisms linking SDB and chronic health conditions. To date, most epidemiologic studies of risk factors for SDB have been cross-sectional[12-15] and, thus, are of limited value in differentiating primary (causal) from secondary (consequential) relationships. Data also are lacking that address the absolute rate of change in the respiratory disturbance index (RDI) (the metric most commonly used to measure SDB)[16] in population subsets. Longitudinal studies, where both changes in risk factors and changes in SDB are measured prospectively, are more suited for identifying causation and characterizing subsets of individuals who are at increased risk for progression or remission of SDB. They also provide less biased estimates of change in RDI than may be inferred from cross-sectional analyses, which may be influenced by selection, period, cohort, and survivor effects.[17] One recent population-based study reported significant associations between change in weight and level of RDI.[18] This study was restricted to a sample with a relatively narrow age range and ethnic diversity and did not evaluate differences in rates of progression in population subsets. In the current study, we have examined the relationship of measures of SDB, determined at 2 time points, to a variety of potential risk factors, including familial risk of SDB, among subjects with a broad age range and a substantial minority representation.

METHODS

Study Population

The Cleveland Family Study was designed to characterize the natural history and the role of familial factors in SDB and includes families with and without members with diagnosed SDB followed longitudinally.[19,20] The sample consisted of 386 White and 100 Black subjects, each studied twice, 5.3 ± 0.9 (SD) years apart. Briefly, "index" families were identified through a proband with laboratory-confirmed SDB identified at 1 of 3 university-affiliated sleep laboratories. Eligibility criteria for index probands included an RDI of at least 20 (for adults) or at least 5 (children, aged < 18 years) or severe enough to warrant therapy; absence of substantial comorbidity; and residence of at least 2 first-degree relatives within the Greater Cleveland area. During the first 5 study years, control families also were studied (later, the study included index families only). Control families were chosen randomly from a list of names provided by the index proband of neighbors or friends who resided in the same neighborhood as the index case and had at least 3 living relatives available to study. The cohort also included family members (available

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first-degree relatives and spouses and selected second-degree relatives) of both index cases and controls. Subjects identified as SDB probands (N=55) and any other subject who had received a specific treatment for SDB any time during the follow-up period (N=27) were excluded from this analysis to eliminate effects due to treatment or referral biases. Thus, the analysis sample included members of case and control study families other than index probands or family members who had undergone SDB treatment.

Table 1—Cohort Characteristics: Comparison of Study Subjects to Those Not Followed Up. Cleveland Family Study, 1990-2000

	Cohort	Not Followed up	*P* value
N	486	168	
Age, mean ± SD	31.6 ± 17.9	30.8 ± 18.8	.96
Sex			
Female, N (%)	289 (59.5)	79 (47.0)	<.01
Race, N (%)			
Black	100 (20.6)	55 (32.7)	.10
Other†	386 (79.4)	113 (67.3)	
Family Recruitment			
From index family member, N (%)	299 (61.5)	94 (56.0)	.34
Current Loud Snoring			
Yes, N (%)	142 (29.4)	39 (24.1)	.31
Initial RDI, median (IQR)	2.6 (1.1,5.8)	2.5 (1.1, 6.7)	.61*
Baseline BMI, median (IQR)	25.7 (21.5, 30.8)	24.1 (20.4, 28.4)	.08*

RDI, respiratory disturbance index**;** IQR, interquartile range; BMI, body mass index; †98% White; 2% Hispanic or mixed ethnicity, *p-value based on log transformed values.

Table 2—Distribution of Baseline and Follow-up Time-Dependent Variables by Sex. Cleveland Family Study, 1990-2000

	Males			Females			All		
	Baseline	Follow-up	P value	Baseline	Follow-up	P value	Baseline	Follow-up	P value
RDI ≥ 5, %	39.1	52.8	<.01	22.2	34.6	<.01	29.0	42.0	<.01
RDI ≥ 15, %	13.7	23.4	<.01	8.3	11.4	.13	10.5	16.3	<.01
RDI, median (IQR)	3.7 (1.6, 8.1)	5.4 (1.9, 13.9)	<.01	2.0 (0.9, 4.7)	3.0 (1.1, 6.8)	<.01	2.6 (0.9, 4.7)	3.6 (1.1, 6.8)	<.01
Age, mean ± SD, years	29.5 ± 18.4	34.9 ± 18.6	<.01	33.0 ± 17.5	38.4 ± 17.5	<.01	31.6 ± 17.9	37.0 ± 18.0	<.01
BMI, kg/m², mean ± SD	25.4 ± 6.8	27.7 ± 7.4	<.01	27.5 ± 8.2	29.6 ± 8.6	<.01	26.7 ± 7.7	28.8 ± 8.2	<.01
Alcohol Consumption, Weekly or more, %	23.2	19.1	.12	8.9	8.1	.58	14.7	12.5	.14
Current Smoking, %	19.1	27.8	<.01	21.1	23.5	.12	20.3	25.3	<.01
Cardiovascular Disease, %	4.6	9.1	<.01	2.8	6.6	<.01	3.5	7.6	<.01
Hypertension, %	16.7	17.8	.72	14.4	19.7	<.01	15.3	18.9	.04
Diabetes, %	1.0	2.0	.31	3.2	5.2	.01	2.3	3.9	<.01

P values adjusted for familial clustering and repeated measures; RDI, respiratory disturbance index; BMI, body mass index; IQR, interquartile range

Protocol and Measurements

The study visits have been described in detail.[19,20] Briefly, trained research assistants studied families at home or other convenient locations. Nearly identical protocols were followed at baseline and at the 5-year follow-up examination. Medical and family history, medication use, race, and symptoms were assessed with the Children's Sleep and Health Questionnaire or the Adult Health and Sleep Study Questionnaire.[21] Blood pressure was measured in the sitting position in duplicate after a minimum of a 5-minute rest period using a size-appropriate cuff (readings that did not agree within 4 mm were repeated with a third reading). Height and weight were measured by a standardized protocol. Overnight in-home sleep monitoring was performed with an Edentrace I or II monitor (Eden Prairie, Minn) measuring airflow (nasal/oral thermistry), chest wall impedance, finger pulse oximetry, and heart rate. Respiratory events were defined as cessations (apneas) or discrete reductions (hypopneas) in airflow or chest impedance, lasting at least 10 seconds and associated with at least a 2.5% fall in oxygen saturation. Sleep time was estimated from inspection of the sleep record and subject-completed sleep diary. The RDI was determined by dividing the number of respiratory events by the estimated hours of sleep time. Consistency of scoring over the course of the study was achieved by ongoing quality-assurance exercises, with blinded rescoring by research staff, and review of all studies by a single reviewer (SR). The intraclass correlation coefficient for the RDI from 28 randomly selected studies initially scored in the first 5 years and rescored in the 12th study year by a different scorer was 0.971. In our past work, we showed that the RDI from the in-home studies had an excellent correlation with that derived from full in-laboratory polysomnography.[22] In the last 18 months, we also assessed the comparability of this measure to the RDI produced by 12-channel in-laboratory polysomnography (by a Compumedics E Series System, using a recording montage consisting of C_3/A_2 and C_4/A_1 electroencephalograms, right and left electrooculograms, a bipolar submental electromyogram, thoracic and abdominal respiratory inductance plethysmography, airflow measured by nasal-oral thermocouple and nasal pressure, finger pulse oximetry, electrocardiogram, body position by a mercury gauge sensor, and bilateral leg movements by piezosensors) in 169 Cleveland Family Study participants undergoing both assessments with a maximum of 1

Table 3—Median Change (IQR) in Respiratory Disturbance Index by Sex and Baseline Characteristics. Cleveland Family Study, 1990-2000

	Males				Females				All			
	N	Initial RDI	Final RDI	5-year Δ RDI†	N	Initial RDI	Final RDI	5-year Δ RDI†	N	Initial RDI	Final RDI	5-year Δ RDI†
Age, years												
≤18	71	1.8 (0.9, 3.8)	1.9 (0.9, 3.8)	0.2 (-1.1, 1.9)	78	1.6 (0.7, 3.1)	1.4(0.6, 2.6)	-0.2 (-1.2, 1.0)	149	1.8 (0.8, 3.3)	1.7 (0.8, 3.1)	-.1 (-1.1, 1.3)
19-40	77	3.7 (1.7, 6.5)	6.6 (3.4, 13.9)	1.6 (-0.4, 7.4)	116	1.6 (0.8, 3.8)	2.7 (1.0, 6.6)	0.9 (-0.4, 4.5)	193	2.4 (1.0, 4.8)	4.2 (1.5, 8.8)	1.1 (-0.4, 6.1)
41-54	26	7.5 (3.6, 23)	13.9 (6.1, 34.2)	5.2 (-0.7, 12.9)	61	2.1 (1.0, 7.0)	4.5 (2.2, 9.1)	1.7 (-1.6,5.8)	87	3.0 (1.3, 10.0)	6.3 (2.9, 15.7)	2.3 (-1.6, 7.0)
55+	23	9.7 (5.7,20.9)	17.0 (9.1, 24.8)	1.1 (-1.8, 10.4)	34	7.3 (3.9, 18.9)	9.9 (6.1, 20.6)	0.4 (-3.5,8.8)	57	8.5 (4.7, 18.9)	13.1 (6.5, 21.5)	0.9 (-3.0, 8.9)
		P<.01	*P*<.01	*P*<.01		*P*<.01	*P*<.01	*P*<.01		*P*<.01	*P*<.01	*P*<.01
BMI, kg/m²												
< 21.5	54	1.8 (0.9, 2.8)	1.6 (0.9, 2.8)	0 (-1.6, 1.2)	66	1.3 (0.7, 2.5)	1.2 (0.5, 2.4)	-0.1 (-1.1, 0.9)	120	1.5 (0.8, 2.7)	1.3 (0.7, 2.6)	-0.1 (-1.1, 1.1)
21.5 - 25.69	47	2.4 (1.5, 4.7)	4.3 (2.3, 8.0)	2.1 (-0.7, 5.2)	75	1.4 (0.7, 3.1)	2.1 (0.7, 4.7)	0.6 (-0.7, 2.2)	122	1.7 (0.8, 3.6)	2.9 (1.1, 6.3)	0.9 (-0.7, 3.4)
25.70 - 30.74	58	5.4 (3.7, 9.6)	8.3 (4.9, 16.5)	1.6 (-1.2, 7.2)	61	2.6 (1.3, 5.1)	3.6 (1.8, 6.2)	1.5 (-1.1, 3.8)	119	3.9 (1.8, 8.1)	5.5 (2.9, 12.2)	1.5 (-1.2, 5.8)
30.75+	35	11.2 (4.3, 33.2)	24.7 (13.9, 43.0)	9.7 (-2.1, 16.5)	86	4.1 (1.4, 10.9)	7.6 (3.4, 17.4)	2.3 (-1.8, 8.3)	121	4.8 (1.9, 17.3)	10.1 (4.4, 23.6)	2.8 (-1.8, 11.2)
		P<.01	*P*<.01	*P*<.01		*P*<.01	*P*<.01	*P*=.02		*P*<.01	*P*<.01	*P*<.01

P-values based on Kruskal-Wallis – Wilcoxon nonparametric analyses; IQR, interquartile range; RDI, respiratory disturbance index; BMI, body mass index; † 5-year Δ RDI; Median 5-year difference in RDI (5*(ΔRDI/follow-up time))

week between studies. The in-laboratory studies were scored blinded to the results of the in-home studies using Sleep Heart Health criteria (modified to include nasal pressure change for hypopnea detection) and applying a 3% desaturation criteria for event identification.[23] The RDIs collected with the different equipment and scored by different criteria showed excellent levels of agreement, with an intraclass correlation coefficient of 0.83. Considering the in-laboratory RDI as the "gold standard" and an AHI of at least 5 as "positive," the in-home RDI provided a sensitivity of 84% and specificity of 90%.

The protocol was approved by the Institutional Review Boards of the hospitals from which probands were recruited, and written informed consent was obtained for all subjects.

Definitions

Hypertension was considered present if, for individuals aged greater than 16 years, systolic blood pressure was at least 140 or diastolic blood pressure was at least 90, or the subject reported use of antihypertensive medication. For children aged 16 years or younger, age-specific thresholds of HTN were used.[24] Cardiovascular disease was considered present if the subject reported having had a heart attack, angina, stroke, or heart failure. Diabetes was based on physician-diagnosed diabetes. Current smoking was based on an affirmative response to smoking at least 1 cigarette per day in the prior month, and current alcohol to drinking at least 1 alcoholic drink per week. "Family risk" was considered "high" if the subject had been recruited as a first-degree or second-degree relative of an index proband or was a relative of a control proband with an RDI of at least 15.

Table 4—Estimated Baseline Respiratory Disturbance Index and Change in Respiratory Disturbance Index* per 5-Year Age Increase by Baseline Age, Body Mass Index, and Sex

Men					Women				
Age	BMI	Baseline RDI (95% CI)	Absolute Change in RDI (95% CI)	Percentage Change in RDI (95% CI)	Age	BMI	Baseline RDI (95% CI)	Absolute Change in RDI (95% CI)	Percentage Change in RDI (95% CI)
20	22	1.6 (1.2, 2.0)	0.1 (-0.3, 0.4)	3.9 (-14.9, 26.9)	20	22	0.8 (0.6, 1.1)	0.0 (-0.1, 0.2)	5.7 (-12.5, 27.8)
20	26	2.3 (1.8, 2.9)	0.2 (-0.3, 0.7)	8.9 (-11.3, 33.7)	20	26	1.1 (0.8, 1.4)	0.1 (-0.1, 0.3)	10.8 (-8.9, 34.7)
20	30	3.0 (2.3, 4.0)	0.5 (-0.3, 1.2)	14.9 (-8.2, 43.8)	20	30	1.3 (1.0, 1.7)	0.2 (-0.1, 0.5)	16.9 (-5.6, 44.9)
20	34	3.8 (2.7, 5.4)	0.8 (-0.3, 1.9)	21.0 (-6.1, 55.9)	20	34	1.5 (1.1, 2.0)	0.4 (-0.1, 0.8)	23.1 (-3.4, 56.9)
30	22	1.7 (1.3, 2.2)	0.4 (0.0, 0.8)	23.4 (1.9, 49.5)	30	22	0.7 (0.5, 0.9)	0.2 (0.0, 0.3)	24.9 (6.3, 46.6)
30	26	2.6 (2.1, 3.3)	0.7 (0.1, 1.3)	27.4 (6.0, 53.0)	30	26	1.0 (0.8, 1.3)	0.3 (0.1, 0.5)	28.8 (10.3, 50.5)
30	30	4.0 (3.2, 5.0)	1.3 (0.4, 2.2)	32.6 (10.5, 59.2)	30	30	1.4 (1.1, 1.8)	0.5 (0.2, 0.8)	34.2 (14.7, 56.9)
30	34	5.9 (4.5, 7.6)	2.2 (0.8, 3.6)	38.0 (14.3, 66.6)	30	34	2.0 (1.6, 2.5)	0.8 (0.4, 1.2)	39.6 (18.6, 64.4)
40	22	2.3 (1.6, 3.1)	0.8 (0.2, 1.4)	36.5 (11.1, 67.7)	40	22	0.9 (0.7, 1.2)	0.3 (0.1, 0.5)	37.3 (16.1, 62.3)
40	26	3.4 (2.7, 4.3)	1.3 (0.5, 2.2)	38.6 (13.7, 69.0)	40	26	1.3 (1.0, 1.6)	0.5 (0.2, 0.8)	39.4 (18.8, 63.6)
40	30	5.6 (4.5, 7.0)	2.4 (1.0, 3.8)	42.5 (16.9, 73.5)	40	30	1.9 (1.6, 2.4)	0.8 (0.4, 1.2)	43.3 (22.1, 68.0)
40	34	9.0 (7.0, 11.5)	4.2 (1.8, 6.5)	46.5 (19.9, 78.9)	40	34	2.9 (2.4, 3.5)	1.4 (0.7, 2.0)	47.3 (25.3, 73.2)
50	22	3.6 (2.5, 5.1)	1.5 (0.4, 2.5)	40.4 (11.6, 76.7)	50	22	1.7 (1.3, 2.2)	0.7 (0.3, 1.1)	40.4 (15.3, 70.9)
50	26	5.0 (3.8, 6.5)	2.0 (0.6, 3.4)	40.4 (12.9, 74.6)	50	26	2.1 (1.6, 2.6)	0.8 (0.4, 1.3)	40.4 (17.6, 67.6)
50	30	8.0 (6.3, 10.2)	3.4 (1.2, 5.6)	42.4 (13.8, 78.1)	50	30	3.0 (2.4, 3.8)	1.3 (0.6, 2.0)	42.3 (19.1, 70.1)
50	34	13.1 (10.0, 17.3)	5.9 (1.9, 9.8)	44.7 (14.2, 83.3)	50	34	4.6 (3.7, 5.7)	2.1 (0.9, 3.2)	44.6 (19.8, 74.6)
60	22	6.5 (4.2, 10.0)	2.2 (-0.2, 4.7)	34.4 (-0.6, 81.9)	60	22	3.8 (2.6, 5.5)	1.3 (-0.1, 2.6)	33.6 (0.5, 77.6)
60	26	7.5 (5.5, 10.1)	2.4 (-0.0, 4.8)	32.3 (0.6, 74.2)	60	26	3.9 (2.9, 5.1)	1.2 (0.1, 2.3)	31.5 (3.3, 67.4)
60	30	11.1 (8.2, 15)	3.6 (0.0, 7.2)	32.4 (0.2, 75.0)	60	30	5.2 (4.0, 6.8)	1.6 (0.2, 3.1)	31.6 (4.2, 66.2)
60	34	17.5 (12.2, 25)	5.8 (-0.5, 12)	33.0 (-1.4, 79.3)	60	34	7.5 (5.7, 10.0)	2.4 (0.2, 4.6)	32.1 (3.3, 69.0)

BMI, body mass index; CI, confidence interval; RDI, respiratory disturbance index**;** *Adjusted for age, BMI, race, high familial risk, and all covariates in the multivariate model, and familial clustering.

Table 5—Estimated Baseline Respiratory Disturbance Index and Change in Respiratory Disturbance Index* per 5% Increase in Body Mass Index by Baseline Age, Body Mass Index, and Sex.

Men					Women				
Age	BMI	Baseline RDI (95% CI)	Absolute Change in RDI (95% CI)	Percentage Change in RDI (95% CI)	Age	BMI	Baseline RDI (95% CI)	Absolute Change in RDI (95% CI)	Percentage Change in RDI (95% CI)
20	22	1.6 (1.2, 2.0)	0.1 (0.0, 0.2)	7.7 (1.1, 14.7)	20	22	0.8 (0.6-1.1)	0.0 (-0.0, 0.1)	1.8 (-3.9, 7.9)
20	26	2.3 (1.8, 2.9)	0.2 (0.1, 0.4)	9.7 (3.4, 16.5)	20	26	1.1 (0.8, 1.4)	0.0 (-0.0, 0.1)	3.7 (-1.8, 9.6)
20	30	3.0 (2.3, 4.0)	0.4 (0.1, 0.6)	12.4 (5.1, 20.1)	20	30	1.3 (1.0, 1.7)	0.1 (-0.0, 0.2)	6.2 (-0.3, 13.2)
20	34	3.8 (2.7, 5.4)	0.6 (0.2, 1.0)	15.4 (6.3, 25.3)	20	34	1.5 (1.1, 2.0)	0.1 (-0.0, 0.3)	9.1 (0.6, 18.3)
30	22	1.7 (1.3, 2.2)	0.2 (0.0, 0.3)	9.9 (2.3, 18.0)	30	22	0.7 (0.5, 0.9)	0.0 (-0.0, 0.1)	3.9 (-2.6, 10.8)
30	26	2.6 (2.1, 3.3)	0.3 (0.1, 0.5)	13.3 (6.7, 20.4)	30	26	1.0 (0.8, 1.3)	0.1 (0.0, 0.1)	7.1 (1.6, 12.9)
30	30	4.0 (3.2, 5.0)	0.7 (0.3, 1.0)	16.6 (9.7, 24.0)	30	30	1.4 (1.1, 1.8)	0.1 (0.1, 0.2)	10.3 (4.5, 16.3)
30	34	5.9 (4.5, 7.6)	1.2 (0.6, 1.7)	19.8 (11.8, 28.4)	30	34	2.0 (1.6, 2.5)	0.3 (0.1, 0.4)	13.3 (6.3, 20.7)
40	22	2.3 (1.6, 3.1)	0.3 (0.0, 0.5)	11.1 (2.7, 20.2)	40	22	0.9 (0.7, 1.2)	0.0 (-0.0, 0.1)	5.0 (-2.0, 12.6)
40	26	3.4 (2.7, 4.3)	0.5 (0.2, 0.9)	16.0 (8.4, 24.1)	40	26	1.3 (1.0, 1.6)	0.1 (0.0, 0.2)	9.7 (3.7, 16.0)
40	30	5.6 (4.5, 7.0)	1.1 (0.6, 1.7)	20.0 (12.1, 28.5)	40	30	1.9 (1.6, 2.4)	0.3 (0.1, 0.4)	13.4 (7.2, 20.1)
40	34	9.0 (7.0, 11.5)	2.1 (1.1, 3.1)	23.3 (14.2, 33.1)	40	34	2.9 (2.4, 3.5)	0.5 (0.2,0.7)	16.5 (9.1, 24.4)
50	22	3.6 (2.5, 5.1)	0.4 (0.0, 0.8)	11.3 (2.1, 21.5)	50	22	1.7 (1.3, 2.2)	0.1 (-0.0, 0.2)	5.3 (-2.4, 13.5)
50	26	5.0 (3.8, 6.5)	0.9 (0.4, 1.4)	17.7 (9.3, 26.7)	50	26	2.1 (1.6, 2.6)	0.2 (0.1, 0.4)	11.3 (4.8, 18.1)
50	30	8.0 (6.3, 10.2)	1.8 (0.9, 2.7)	22.3 (13.2, 32.2)	50	30	3.0 (2.4, 3.8)	0.5 (0.2, 0.7)	15.6 (8.6, 23.1)
50	34	13.1 (10, 17.3)	3.4 (1.6, 5.1)	25.7 (14.9, 37.5)	50	34	4.6 (3.7, 5.7)	0.9 (0.4, 1.3)	18.8 (10.2, 28.1)
60	22	6.5 (4.2, 10.0)	0.7 (-0.2, 1.5)	10.5 (-0.9, 23.3)	60	22	3.8 (2.6, 5.5)	0.2 (-0.2, 0.6)	4.5 (-5.1, 15.1)
60	26	7.5 (5.5, 10.1)	1.4 (0.4, 2.3)	18.3 (7.8, 29.8)	60	26	3.9 (2.9, 5.1)	0.5 (0.1, 0.8)	11.8 (3.5, 20.8)
60	30	11.1 (8.2, 15.0)	2.6 (1.1, 4.1)	23.6 (12.2, 36.0)	60	30	5.2 (4.0, 6.8)	0.9 (0.3, 1.4)	16.8 (7.9, 26.5)
60	34	17.5 (12.2, 25)	4.7 (1.8, 7.6)	27.0 (13.6, 42.0)	60	34	7.5 (5.7, 10.0)	1.5 (0.6, 2.4)	20.0 (9.1, 32.0)

BMI, body mass index; CI, confidence interval; RDI, respiratory disturbance index**;** *Adjusted for age, BMI, race, high familial risk, and all covariates in the multivariate model and familial clustering

Statistical Analysis

Median and interquartile range of initial RDI, final RDI, and 5-year change in RDI (ΔRDI) were examined in univariate fashion according to categories of baseline demographic and clinical factors and compared using the Kruskal Wallis nonparametric test. To adjust for small variations in lengths of follow-up, 5-year ΔRDI was calculated as the annual change in RDI based on exact time between visits, multiplied by 5. In tables presenting univariate associations, body mass index (BMI) was categorized by quartiles; age was classified as 18 years or less (children), 19 to 40 years (young adults), 41 to 54 (mid-aged adults, including generally premenopausal women), and 55 years or older (older adults). Sleep-disordered breathing was also described by use of 2 commonly used cutoff levels (RDI ≥ 5 and RDI ≥ 15, which are mild and more moderate disease, respectively).[16] Analyses of continuous variables were adjusted for family clustering using linear mixed models (SAS Proc Mixed) with family as a random effect or, when analyzing changes over time, random effects for family and individual. Similar analyses of binary outcomes used a generalized estimating equations approach (SAS Proc Genmod) with an exchangeable within-family correlation structure and a robust variance estimate. In multivariate models, the natural logarithms of RDI and BMI were used to achieve distributions that approached normality, where the constant 0.2 was added to the RDI before taking logs to avoid logarithms of 0.

A mixed-effects repeated-measures model was used to jointly estimate cross-sectional and longitudinal effects of gender, age, BMI, and other

covariates on baseline level and change in log-transformed RDI. The cross-sectional model describes the relationship of log(RDI) to covariates at baseline, and the longitudinal model relates changes in log(RDI) to baseline covariates and changes in time-varying covariates. An initial model was constructed considering only race, gender, and family risk as baseline covariates and considering linear, quadratic, and cubic terms of age and log(BMI) as well as their cross products and interactions with sex as time-varying covariates. Other baseline covariates and time-varying covariates such as smoking or alcohol use were then evaluated by testing whether they added significantly to the initial model. The Akaike Information Criterion was used to guide inclusion of terms in the model.[25] The absolute ΔRDI over 5 years was estimated as the product of the antilogarithm of the estimated mean log(RDI) at baseline multiplied by the estimated percentage ΔRDI over 5 years, and its variance was estimated using the delta method.

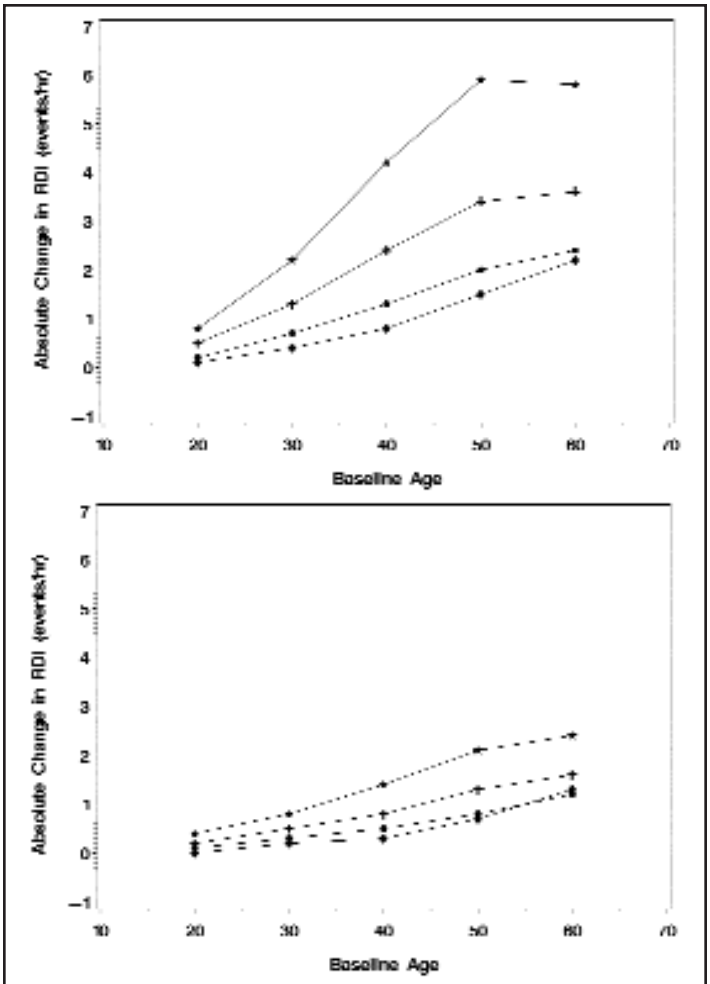
RESULTS

The characteristics of the study sample are shown in Table 1. Of 654 subjects eligible for inclusion in this analysis (ie, due for a 5-year follow-up visit and not under SDB treatment), 486 (74%) had a follow-up visit and thus were included in this analysis. Of those without a follow-up visit, 10 had died, 3 were hospitalized or incapacitated, 28 could not be located, 39 moved out of state, and the remaining 88 refused part or all of the follow-up examination. The sample was 60% female, 21% Black, and predominantly (62%) individuals recruited as a family member of an index proband. Compared to those who did not undergo follow-up sleep monitoring, subjects in the current analysis were of comparable age; had similar baseline levels of RDI, BMI, and snoring frequencies; and represented similar proportions of "index" and control families.

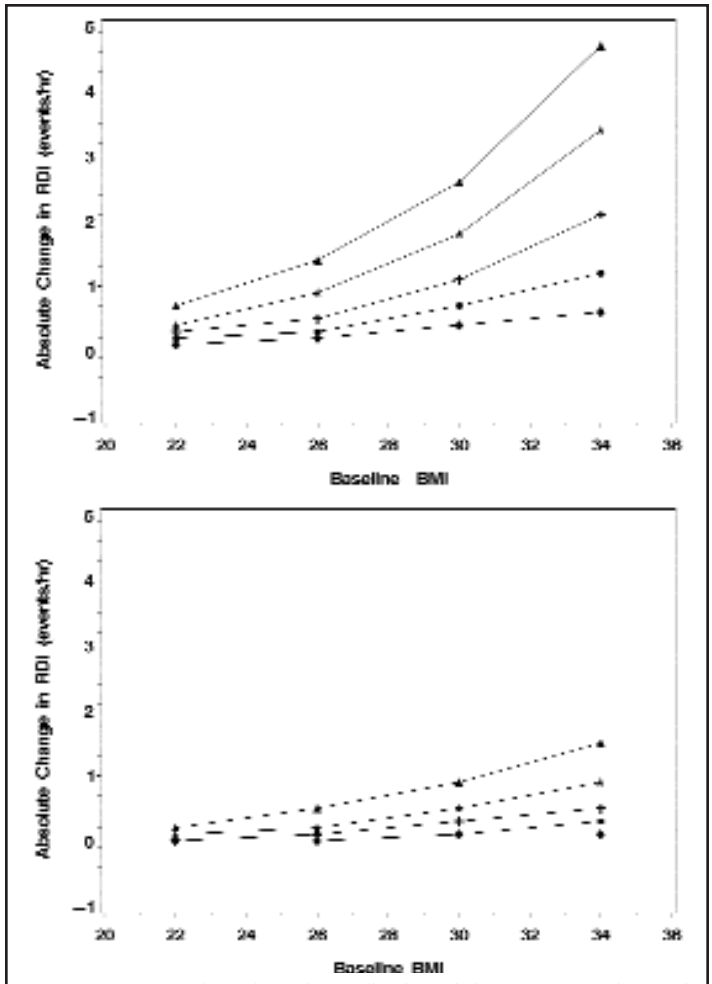
At baseline examination, females were slightly older and had a higher BMI than the males, but had a lower RDI (Table 2). Over the follow-up period, mean BMI of subjects increased by approximately 2 kg/m^2, with males and females showing similar increases (Table 2). The overall baseline prevalences of CVD and diabetes were relatively low and approximately doubled over the follow-up period (to 7.6% and 3.9%, respectively). The HTN prevalence increased from 15.3% to 18.9%, with the largest percentage increase observed for females. Prevalence of smoking increased, primarily in males; average self-reported alcohol consumption did not change.

Over the follow-up period, the median RDI increased by 38% (from 2.6 to 3.6), and the percentage of subjects with SDB, as identified by an RDI of at least 15, increased from 10.5% to 16.3% (Table 2*)*. The prevalence of SDB among men increased significantly (from 13.7% to 23.4%, $P<0.01$), and in women increased from 8.3% to 11.4% ($P=0.13$).

The variation in RDI and absolute ΔRDI with age, gender, and BMI is shown in Table 3. Cross-sectional RDI levels at both time points were higher in older as compared with younger individuals. The ΔRDI also varied by age, with RDI showing little change among females first studied when they were 18 years of age or younger and increasing the most in subjects first studied between the ages of 19 and 54 years. At all ages, both cross-sectional levels and absolute ΔRDI were higher in males than females. Baseline, follow-up, and ΔRDI increased in a nonlinear pattern with increasing BMI. No increase in ΔRDI was observed in the subject group with BMI values of 21.5 or less. Median ΔRDI was significantly



Figures 1a and 1b—Change in respiratory disturbance index (RDI) per 5-year increase in age. The predicted absolute change in RDI per 5-year age increment is illustrated for males (1a) and females (1b) according to baseline age (x axis) and baseline body mass index(BMI) (♦BMI 22 kg/m^2; • BMI 26 kg/m^2; : BMI 30 kg/m^2, H BMI 34 kg/m^2). Estimates are derived from the multivariate model, incorporating all main and interaction effects.



Figures 2a and 2b— Change in respiratory disturbance index (RDI) per 5% increase in body mass index (BMI). The predicted absolute change in RDI per 5% change in BMI is illustrated for males (2a) and females (2b) according to baseline BMI (x axis) and baseline age (♦age 20; • age 30, : age 40, H 50, ≤60. Estimates are derived from the multivariate model, incorporating all main and interaction effects.

higher in those with more obesity (2.8 vs –0.1, $P<0.001$, for the top versus lowest BMI quartile). The RDI levels did not differ by "familial risk" or by race (data not shown).

In unadjusted analyses, cross-sectional levels of RDI at both time points were significantly higher for those with CVD or HTN than those without these conditions (median baseline and follow-up RDI: 7.5 and 12.8, vs 2.5 and 3.5, for those with and without CVD; $P=.01$; median baseline and follow-up RDI: 6.5 and 10.9, vs 2.3 and 3.1, for those with and without HTN, $P<.01$). The ΔRDI tended to be higher in those individuals with these conditions but did not reach statistical significance. Those with diabetes also tended to have higher cross-sectional levels of RDI and ΔRDI, but differences were not statistically significant.

In multivariate analyses, change in log(RDI) was significantly related to changes in age, age-squared, age-cubed, and changes in log(BMI), log(BMI)-squared, and change in age*log(BMI) (Appendix). Family risk predicted cross-sectional RDI level but not longitudinal change in RDI (ie, those related to an affected proband were estimated to have an RDI 32% [95% CI, 13-53%] higher than those with no affected family member.) Race, forced into the cross-sectional model, was not statistically significant ($P=0.2$). Once these effects were accounted for, alcohol use, CVD, diabetes, and HTN did not predict RDI level or ΔRDI. Smoking status predicted cross-sectional RDI level but not longitudinal change in RDI.

Baseline RDI and longitudinal (within-person) change in RDI, expressed as absolute and percentage changes, for men and women at different baseline ages and BMI levels are estimated from this multivariate model (Tables 4 and 5; Figures 1 and 2). Given the distribution of RDI, it can be seen how small changes in absolute level may produce large percentage changes. Figures 1a and 1b show the estimated absolute change in RDI for 5-year increments of age, according to both baseline age and BMI for the 2 sexes. Estimates of change in RDI vary with baseline age and BMI, with larger age effects observed for older individuals and those with a higher baseline BMI. At any given age and BMI, larger absolute 5-year changes were seen for males as compared with females. For example, in males, a 5-year age increment predicts an increase in RDI of approximately 0.4 for a 30-year-old with a BMI of 22, and 5.8 for a 60-year-old with a BMI of 34. In females, the absolute changes in RDI with a 5-year age increment were approximately half of what were observed for males (eg, 0.2 for a 30-year-old, BMI of 22; 2.4 for a 60-year-old, BMI of 34). However, as a percentage, changes in men and women with 5-year age increments were fairly similar across all levels of baseline age and BMI.

Similarly, the effects of a 5% change in BMI for each sex at different baseline levels of BMI and age are estimated (Figures 2a and 2b). Estimated changes in RDI associated with a 5% increase in BMI vary from approximately less than 0.1 (1.8%) (for a 20-year-old woman, baseline BMI 22) to 4.7 (27%) (for a 60-year-old man, baseline BMI 34). For both sexes, the impact of a change in BMI is again greatest among the oldest and proportionately heaviest individuals, and greater in men than women. At any given baseline BMI and age, an increase in BMI was associated with a 2- to 4-fold higher absolute change in RDI in males than females. Weight gain also was associated with a greater percentage increase in RDI in men as compared with women. For example, at age 40 and at a BMI of 26, a 5% increase in BMI is associated with a 0.1 (9.7%) change in RDI in women and a 0.5 (16.0%) change in men.

DISCUSSION

This report provides the first data that quantify longitudinal changes in RDI across an ethnically diverse cohort with a wide age range. The high follow-up rate and availability of standardized data regarding a number of putative host and environmental risk factors for SDB enabled assessment of the impact of both time-dependent and time-independent risk factors on RDI level. Furthermore, the use of multivariate techniques allowed assessment of the effects of covariates on both level and rate of change of RDI and quantification of gender differences.

To determine the natural history of SDB in a referred sample, analyses were restricted to individuals who had neither presented to a sleep laboratory nor been treated for SDB during the follow-up period. Individuals who present for treatment may have higher levels of comorbidity than nonreferred individuals, limiting inferences to a community sample. Additionally, treatment per se may influence the natural history of the disorder. In this nonreferred sample, RDI increased on average by 30% to 40% over 5 years, and the number of individuals with an RDI of at least 15 increased by approximately 50% (from 10.5% to 16.3%). These data suggest that even among subjects who have not sought medical help for SDB, the RDI tends to increase, and the prevalence of SDB of potential clinical significance also grows. The findings clarify those from previous reports of small, highly selected samples that have reported inconsistent ΔRDI.[26-29] Those studies, however, included patients with high degrees of SDB who refused treatment and were followed for variable lengths of time. A more complete analysis of "incident" SDB (occurring in individuals initially free of SDB) is dealt with in more detail in another manuscript.[30]

Our sampling strategy may have produced biased estimates of longitudinal change. By excluding subjects who had been referred to a sleep laboratory or had received SDB treatment, we may have excluded individuals with the most severe and, possibly, the most progressive disease. However, it was our intent to quantify SDB progression among a nonreferred sample, since a clinic sample may include a disproportionate number of individuals with comorbidities whose rate of change may not be representative of that in a more general sample. On the other hand, by including family members of index probands, we may have selected a sample with a higher genetic propensity for SDB. However, because only a small number of relatives and controls were excluded because of treatment (N=27) and because familial risk appears to influence baseline RDI but not RDI progression, we think our findings are likely to be generalizable to other samples. This is also supported by the remarkable similarity of our estimates to those obtained in the Wisconsin Sleep Cohort, a sample of middle-aged working adults.[18] In that study, the RDI was calculated using a more stringent hypopnea definition than in our study (with events requiring a 4% rather than a 2.5% desaturation). The prevalence of SDB (defined by an RDI ≥ 15) after 4 years in that study increased by 48% (from 7% to 10%) as compared with our observed increase of 50% (10.5% to 16.3%) after 5 years. The mean 4-year change in RDI in that sample was 1.4 as compared with a 5-year change of 2.5 (9.9 SD) in our sample. We demonstrated similar associations of change in BMI and ΔRDI (among 50-year-olds with a BMI of 30, a 5% weight increase was associated with a 0.5 increase in RDI in women and a 1.8 increase in men, as compared with an increase of approximately 2.0 with a weight gain of 5% to 10% reported for the mixed-sex sample by Peppard et al).[18] However, the Wisconsin study did not fully explore potential sex differences in weight gain on ΔRDI, or nonlinear influences of age and BMI, and did not assess the association of change in RDI with such covariates as familial risk, race, and comorbidity.

Our findings extend those of Peppard and colleagues by showing that the impact of changes in BMI varies according to initial level of BMI, age, and sex and that such effects are nonlinear. For example, the effects of weight gain are greatest for older obese men. A 5% increase in BMI among men aged 60 years with an initial BMI of 34 kg/m^2 is associated with a 4.7 (27%) increase in RDI. In contrast, among young women (aged 20 years) with an initial BMI of 22, a 5% weight gain is associated with only a 1.8% increase in RDI.

Although women were on average proportionately heavier than men, both their absolute and percentage increase in RDI with increased weight was less than that observed in men, regardless of age and baseline BMI. These observations indicate that SDB may be most progressive among older heavier men and suggest the utility of carefully following such individuals after weight gain.

A simple but less efficient alternative modeling approach to the 1 we used would be to fit a cross-sectional model to the baseline log(RDI) values and a separate longitudinal model using the change in log-transformed RDI as the outcome. However, our exploratory work comparing

alternative modeling strategies showed that the estimated variances of parameters from the combined model were lower by 8% to 16% for terms involving age and by 32% to 36% for terms involving BMI, illustrating the improved efficiency of the combined modeling approach. Additionally, we were able to jointly estimate cross-sectional and longitudinal relationships and to estimate with a confidence interval the absolute change in RDI by taking the product of the proportionate change (estimated longitudinally) with the baseline level (estimated cross-sectionally). This parameter of absolute change can be interpreted as median baseline level multiplied by median percentage change. Given the paucity of longitudinal analyses of RDI, understanding how RDI changes both in relative and absolute terms may be important.

Tables 4 and 5 illustrate that reporting percentage changes in RDI without specifying baseline RDI is potentially misleading. On the one hand, large percentage increases may correspond to small clinically unimportant absolute changes. For example, an estimated 37% increase in RDI per 5-year age increase in 40-year-old women with a BMI of 22 corresponds to an absolute change of approximately 0.3 in terms of absolute RDI (Table 5). This is also important to consider when describing sex differences in RDI and ΔRDI. For example, estimated percentage changes in RDI with age are similar for men and women. However, because baseline levels are 2 to 3 times higher for males, it follows that the absolute changes in RDI are much higher for males. Thus, while the driving reasons behind analysis of log-transformed RDI, with resulting emphasis on percentage change, are statistical (to achieve normality and homoscedasticity of residuals), it is crucial for interpretation to translate results to the absolute RDI scale.

Previously, we had reported higher RDI levels in Black as compared with White children, with little or no race differences in RDI levels of older adults.[2,30,31] In the current analysis, we did not demonstrate race differences in ΔRDI over 5 years. Further follow-up will be needed to determine whether elevated levels of RDI in Black children are a predisposing cause for SDB in adulthood.

Adjusted analyses showed that a "high familial risk" for SDB was associated with a 32% greater baseline RDI level. However, familial risk was not associated with longitudinal change in RDI. The higher baseline RDI levels in relatives of subjects with SDB are consistent with previous reports of a familial aggregation of SDB.[20,32] The inability to show an effect of family membership on ΔRDI may have been related to the rather crude measurement of family risk used here or because "familial risk" may influence level but not rate of progression. More precise modeling of familial and/or genetic relationships may shed further light on the role of genes on determining ΔRDI.

Despite the growing evidence that CVD morbidity is increased in people with SDB, the nature of this association is debated. Obesity increases the risk for both CVD and SDB[33] and, thus, could be a confounder. Recent studies, however, have shown that the association of CVD or HTN with SDB persists following adjustment for BMI and other CVD risk factors.[6,10] These findings, in conjunction with animal data showing elevations in blood pressure with experimentally induced upper airway obstruction,[34] have been interpreted as indicating an independent and probably causal role of SDB in the pathogenesis of CVD. Nevertheless, longitudinal data that describe the development of CVD in response to SDB are not available. In the current analyses, CVD, HTN, and diabetes did not predict level or ΔRDI after adjusting for age, sex, and BMI. Because the prevalence of CVD and diabetes was low, it is possible that these negative findings were due to limited statistical power. However, the negative association with HTN, which was found in 19% of the sample at follow-up, provides support to the contention that HTN does not cause SDB.

In addition to the limitations noted above, it should be noted that analyses may be somewhat constrained by potential misclassification of self-reported exposures, such as smoking and alcohol use. Also, any night-to-night variability in the measurement of SDB will reduce the ability to precisely estimate long-term longitudinal changes. Given the interest in maintaining comparability of longitudinal measurements over time, we used definitions and technology for measuring the RDI that were constant over the 10 years of data collection, allowing for unbiased assessments of change in SDB over time. Newer technologies (eg, nasal pressure sensors) may allow detection of more apneas, as compared with other sensors, and could influence the exact number of respiratory events measured at each time point, although they are unlikely to influence estimates of the difference in the number of events over time. When comparing data collected using the in-home technology to state-of-the-art polysomnography, we did indeed observe the latter methods to identify more events (ie, the in-home studies had a sensitivity of 84%). However, the excellent levels of agreement between the 2 techniques (intraclass correlation coefficient 0.83), which are in the range reported for night-to-night variability for full polysomography,[35] indicate that the different methods produce estimates of RDI that are highly comparable.

In summary, these findings demonstrate that the "natural history" of SDB includes a moderate level of progression, findings that were observed even among subjects whose symptoms did not lead to referral to a sleep center. The findings highlight the variation of longitudinally determined measures of RDI with age and BMI, with larger changes (especially those related to weight change) observed in men than in women.

APPENDIX

Parameter estimates from combined cross-sectional and longitudinal mixed effects model

	Estimate	SE	*P*-value
Cross-sectional terms:			
Intercept	0.3098	0.0952	0.002
Sex (1=male, 0=female)	0.8994	0.1087	<0.0001
Familial risk (1=yes, 0=no)	0.2788	.0761	0.0003
Race (1=black, 0=other)	-0.1294	0.1012	0.20
AGE1	0.01993	0.00534	0.0002
$(AGE1)^2$	0.00112	0.00021	<0.0001
$(AGE1)^3$	-7.91×10^{-6}	6.88×10^{-6}	0.25
LNBMI1	2.2261	0.2954	<0.0001
$(LNBMI1)^2$	1.7945	0.8205	0.03
$(LNBMI1)^3$	-2.6705	1.4045	0.06
AGE1*LNBMI1	0.03895	0.01569	0.013
Sex*AGE1	0.00662	0.00543	0.22
Sex*LNBMI1	0.7208	0.3474	0.04
Sex*$(AGE1)^2$	-0.00061	0.00022	0.005
AGE1*$(LNBMI1)^3$	-0.1141	0.0572	0.05
AGE1*$(LNBMI1)^2$	0.1330	0.0464	0.004
$(AGE1)^2$*LNBMI1	-0.00242	0.00067	0.0003
Longitudinal terms:			
AGEC-AGE1	0.05568	0.01580	0.0005
$(AGEC)^2$ -$(AGE1)^2$	0.00101	0.00050	0.04
$(AGEC)^3$-$(AGE1)^3$	-0.00002	0.000012	0.03
LNBMIC-LNBMI1	1.6618	0.5655	0.004
$(LNBMIC)^2$-$(LNBMI1)^2$	2.1974	0.9028	0.015
$(LNBMIC)^3$ -$(LNBMI1)^3$	-1.0670	1.0973	0.33
(AGEC*LNBMIC)-(AGE1*LNBMI1)	0.05062	0.02458	0.04
Sex*(AGEC-AGE1)	-0.00214	0.02160	0.92
Sex*(LNBMIC-LNBMI1)	1.1531	0.6994	0.10
Sex*$(AGEC)^2$-Sex*$(AGE1)^2$	0.000060	0.000573	0.92
AGEC*$(LNBMIC)^3$-AGE1*$(LNBMI1)^3$	-.08499	.05803	0.14
AGEC*$(LNBMIC)^2$-AGE1*$(LNBMI1)^2$	.05193	0.04310	0.22
$(AGEC)^2$*LNBMIC-$(AGE1)^2$*LNBMI1	-0.00094	.001101	0.39

AGE1=baseline age (years) –34; AGEC=Current age (years) – 34
LNBMI1= log(baseline BMI)–3.29; LNBMIC = log(Current BMI)–3.29

The combined cross-sectional model for baseline respiratory disturbance index (RDI) and longitudinal model for change in RDI (lower half), with terms chosen by the Akaike Information Criterion. Parallel terms involving sex, age, and body mass index were included in both longitudinal and cross-sectional models so that the longitudinal model can be obtained by differencing the cross-sectional model (17). That is, the terms in the 2 models have comparable interpretations in the absence of period effects, cohort effects, and selection biases. As an example of calculating the estimated group differences, one can see that the estimated regression coefficient of 0.2788 for familial risk implies that those related to a proband have RDIs higher by $(e^{0.2788} - 1) \times 100 = 32\%$ (95% CI, 13-53%) compared to those not related to a proband.

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