Weight Reduction and Increased Physical Activity to Prevent the Progression of Obstructive Sleep Apnea: A 4-Year Observational Postintervention Follow-up of a Randomized Clinical Trial

Obstructive sleep apnea (OSA) has become a major health burden in affluent populations. It is a chronic, progressive disease, and it is well documented that severe OSA is associated with increased cardiovascular morbidity and mortality.[1-3] Obesity is the most important risk factor for OSA; in fact, most patients with OSA are obese.[4] Weight reduction has been shown to improve OSA or even cure it.[5,6] However, whether beneficial changes related to weight loss are maintained after stopping the active lifestyle intervention, and, thus, the progression of OSA prevented, is not known. The aim of the study was to assess the long-term efficacy of a lifestyle intervention based on weight reduction, healthy diet, and physical activity during a 4-year postintervention follow-up in people with OSA who originally participated in a 1-year randomized, clinical lifestyle intervention trial.[5]

Methods. Altogether, 81 consecutive obese adults with mild OSA were randomized into either an intervention group or a control group (eFigure; http://www.jamainternalmed.com). Individuals in the intervention group received a 1-year lifestyle intervention[5] (based on healthy diet and physical activity counseling), including an initial intensive weight reduction program with 12 weeks on a very low calorie diet. The control group received 3 general dietary and exercise counseling sessions. The participants underwent nocturnal cardiorespiratory monitoring using the Embletta polysomnography device (Embla), in accordance with accepted guidelines for diagnosing OSA.[7] The design of the study and lifestyle counseling have been reported previously in detail.[5] During the subsequent 4 years, active counseling was no longer offered. The change in apnea-hypopnea index (AHI) was the main objective outcome variable. The study protocol was approved by the research ethics committee of the Hospital District of Northern Savo, Kuopio, Finland. The participants were given both oral and written information about the protocol, and they provided a signed informed consent. Differences in changes between the groups were assessed with analysis of covariance. Baseline differences in age, sex, body mass index, and the baseline level of respective variable were taken into account by including these variables as explanatory variables in the model. Kaplan-Meier survival curves were calculated to estimate the probability of the progression of mild OSA to moderate or severe OSA in the 2 groups. Participants who were lost during follow-up were treated as censored observations. All comparisons between the treatment groups were based on the intention-to-treat principle, and all analyses were based on the 57 participants who completed the 4-year follow-up. The study sample size was set in order to achieve 90% power at a 5% significance level to detect a 25% difference in the prevalence of mild OSA between the groups after 5 years.

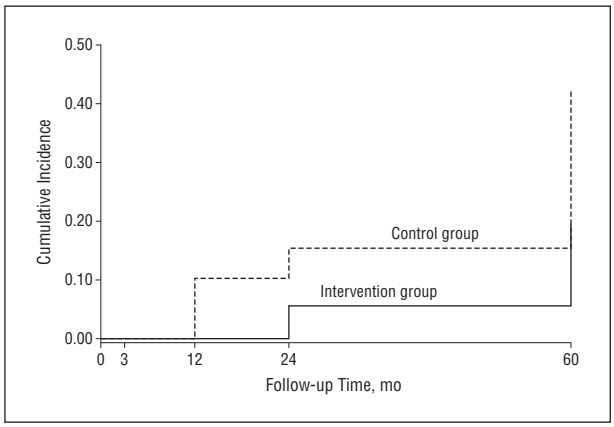

Figure. Progression of obstructive sleep apnea (OSA) by treatment group during the postintervention follow-up period. Kaplan-Meier estimate of probability of progression of OSA. The difference between the survival curves was tested with the log-rank test. The Cox proportional hazard model was used to estimate the hazard ratio for the progression of OSA. There were 14 events in the control group and 6 in the intervention group. The incidence rate for the control group was 0.7 (95% CI, 0.4-1.3), and for the intervention group, 0.3 (95% CI, 0.1-0.7). Log-rank test, $P = .04$. Hazard ratio, 0.39 (95% CI, 0.2-1.0) ($P = .049$).

Results. There were no differences in the characteristics at baseline (eTable 1) and the 12- or 24-month follow-up in individuals who participated in the entire 4-year follow-up compared with those who dropped out earlier. During the 5-year period, the mean change in weight was −5.5 kg (5.5% of the initial weight) in the intervention group and 0.6 kg (0.7% of the initial weight) in the control group ($P = .03$). The changes in AHI between the groups were also significant ($P = .04$) in the intervention group (AHI, −0.8; 95% CI, −3.3 to 1.8) compared with the control group (AHI, 5.0; 95% CI, 0.8 to 9.2) (eTable 2). Over the 4-year follow-up period, the degree of OSA deteriorated from mild to moderate in 6 individuals in the intervention group, all with unsuccessful weight reduction, and in 12 individuals in the control group. Furthermore, the disease deteriorated to severe OSA in 2 people in the control group. The intervention achieved a 61% reduction in the incidence of progression of the OSA compared with the control group (log-rank test $P = .04$) (**Figure**).

Discussion. To our knowledge, this is the first study to provide long-term evidence that a healthy lifestyle along with weight reduction can result in marked improvement of OSA that is sustained even 4 years after the active intervention. Based on current knowledge about the evolution of OSA, weight gain represents a high risk for further progression toward more severe disease, particularly in those patients who already have mild to moderate OSA.[3] This time point is crucial for active intervention since especially severe OSA is known to increase the risk for cardiovascular morbidity and mortality.[1,2] Our results highlight the importance of early detection of OSA and more active treat-

©2013 American Medical Association. All rights reserved.

Downloaded From: http://archinte.jamanetwork.com/ on 07/01/2016

ment of obesity in these patients. It has been estimated that up to 80% to 90% of patients with OSA are undiagnosed,[8] and weight reduction as a treatment of OSA is underrated by many clinicians. There are no national programs for screening OSA or preventing its progression. Thus, there is a definite need for larger, well-controlled trials on the effects of different lifestyle programs among patients with OSA to determine the overall efficacy and long-term success, before large-scale programs may be implemented in clinical settings, as have been done for prevention of type 2 diabetes mellitus, for example.

Henri Tuomilehto, MD, PhD
Juha Seppä, MD, PhD
Matti Uusitupa, MD, PhD
Jaakko Tuomilehto, MD, MA, PhD
Helena Gylling, MD, PhD
for the Kuopio Sleep Apnea Group

Published Online: April 15, 2013. doi:10.1001/jamainternmed.2013.389

Author Affiliations: Oivauni Sleep Clinic, Kuopio, Finland (Dr H. Tuomilehto); Department of Otorhinolaryngology (Dr Seppä) and Clinical Research Center (Drs Uusitupa and Gylling), Kuopio University Hospital, Kuopio, Finland; Institute of Clinical Medicine (Dr Seppä) and Department of Clinical Nutrition, Institute of Public Health and Clinical Nutrition, (Drs Uusitupa and Gylling), University of Eastern Finland, Kuopio; Center for Vascular Prevention, Danube-University Krems, Krems, Austria (Dr J. Tuomilehto); South Ostrobothnia Central Hospital, Seinäjoki, Finland (Dr J. Tuomilehto); and Department of Medicine, Division of Internal Medicine, University of Helsinki, Helsinki, Finland (Dr Gylling).
Correspondence: Dr H. Tuomilehto, Oivauni Sleep Clinic, Puijonkatu 12 B, 70100 Kuopio, Finland (henri.tuomilehto@oivauni.fi).

Author Contributions: Dr H. Tuomilehto had full access to all data in the study and had final responsibility to submit the report for publication. *Study concept and design:* All authors. *Acquisition of data:* H. Tuomilehto, Seppä, and Gylling. *Analysis and interpretation of data:* All authors. *Drafting of the manuscript:* H. Tuomilehto, Seppä, Uusitupa, and Gylling. *Critical revision of the manuscript for important intellectual content:* H. Tuomilehto, Seppä, Uusitupa, J. Tuomilehto, and Gylling. *Statistical analysis:* H. Tuomilehto, Seppä, and J. Tuomilehto. *Obtained funding:* H. Tuomilehto. *Administrative, technical, and material support:* H. Tuomilehto, Uusitupa, and Gylling. *Study supervision:* All authors.
Kuopio Sleep Apnea Group: Grigori Smirnov, MD, PhD, Johanna Sahlman, MD, PhD, Matti Pukkila, MD, PhD, Markku Peltonen, PhD, Tarja Martikainen, MSc, Jouko Kokkarinen, MD, PhD, Jukka Randell, MD, PhD, Esko Vanninen, MD, PhD, Taina Poutiainen, Tomi Laitinen, MD, PhD, Tiina Lyyra-Laitinen, PhD, Ritva Vanninen, MD, PhD, Kari Punnone, MD, PhD, Aki Ikonen, MD, Riitta Pahkala, DD, PhD, Erkki Soini, BSc, and Janne Martikainen.
Conflict of Interest Disclosures: None reported.
Funding/Support: The study was funded by the Hospital District of Northern Savo. Kuopio University Hospital, the Juho Vainio Foundation, Yrjö Jahnsson Foundation, Paulo Foundation, Finnish Cultural Foundation, Finnish Research Foundation of Otology, Finnish Medical Foundation, Respiratory Foundation, and the Finnish Anti-Tuberculosis Foundation have supported the study with grants.
Role of the Sponsors: The funding sources had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.
Online-Only Material: The eFigure and eTables are available at http://www.jamainternalmed.com.
Additional Contributions: Markku Peltonen, MD, assisted with the statistical analyses. Grigori Smirnov, MD, PhD, Matti Pukkila, MD, PhD, Esko Vanninen, MD, PhD, Jouko Kokkarinen, MD, PhD, Jukka Randell, MD, PhD, Johanna Sahlman, MD, PhD, and Tarja Martikainen, MSc, contributed to clinical work related to the study. They also participated in interpreting the results and in editing of the manuscript. All group members approved the current version of the manuscript. The other members of Kuopio Sleep Apnea Group are cordially acknowledged.
Trial Registration: clinicaltrials.gov Identifier: NCT00486746

1. Punjabi NM, Caffo BS, Goodwin JL, et al. Sleep-disordered breathing and mortality: a prospective cohort study. *PLoS Med.* 2009;6(8):e1000132.
2. Marin JM, Carrizo SJ, Vicente E, Agusti AGN. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. *Lancet.* 2005;365(9464):1046-1053.
3. Berger G, Berger R, Oksenberg A. Progression of snoring and obstructive sleep apnoea: the role of increasing weight and time. *Eur Respir J.* 2009;33(2):338-345.
4. Young T, Skatrud J, Peppard PE. Risk factors for obstructive sleep apnea in adults. *JAMA.* 2004;291(16):2013-2016.
5. Tuomilehto HP, Seppä JM, Partinen MM, et al; Kuopio Sleep Apnea Group. Lifestyle intervention with weight reduction: first-line treatment in mild obstructive sleep apnea. *Am J Respir Crit Care Med.* 2009;179(4):320-327.
6. Tuomilehto H, Gylling H, Peltonen M, et al; Kuopio Sleep Apnea Group. Sustained improvement in mild obstructive sleep apnea after a diet- and physical activity-based lifestyle intervention: postinterventional follow-up. *Am J Clin Nutr.* 2010;92(4):688-696.
7. American Academy of Sleep Medicine Task Force. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research: the report of an American Academy of Sleep Medicine Task Force. *Sleep.* 1999;22(5):667-689.
8. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. *Am J Respir Crit Care Med.* 2002;165(9):1217-1239.

Less Is More

Investigation Momentum: The Relentless Pursuit to Resolve Uncertainty

Debate regarding the prostate-specific antigen (PSA) screening test centers around test reliability and whether screening reduces mortality.[1-3] We consider yet another potential downside to the widespread use of unreliable screening tests: the downstream effect of receiving inconclusive or ambiguous

For editorial comment see page 847

results. When receiving information from screening tests, we usually want to know whether the result is a "yes" or a "no." Receiving an inconclusive result amounts to a "don't

©2013 American Medical Association. All rights reserved.

Downloaded From: http://archinte.jamanetwork.com/ on 07/01/2016