California (Dr Lee); Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, Washington (Dr Chen); Preventive and Behavioral Medicine, University of Massachusetts Medical School, Worcester (Dr Ockene); Department of Public Health Sciences, University of California, Davis (Dr Qi); and HealthPartners Research Foundation, Minneapolis, Minnesota (Dr Margolis).

Correspondence: Dr Luo, Department of Community Medicine, Mary Babb Randolph Cancer Center, West Virginia University, PO Box 9190, Morgantown, WV 26506 (Jiluo@hsc.wvu.edu).

Author Contributions: *Study concept and design:* Margolis and Luo. *Acquisition of data:* Rossouw, Ockene, Margolis, and Luo. *Analysis and interpretation of data:* Rossouw, Tong, Giovino, Lee, Chen, Ockene, Qi, Margolis, and Luo. *Drafting of the manuscript:* Rossouw and Luo. *Critical revision of the manuscript for important intellectual content:* Rossouw, Tong, Giovino, Lee, Chen, Ockene, Qi, Margolis, and Luo. *Statistical analysis:* Qi and Luo. *Obtained funding:* Rossouw, Ockene, and Margolis. *Study supervision:* Rossouw and Margolis.

Financial Disclosure: None reported.

1. Willi C, Bodenmann P, Ghali WA, Faris PD, Cornuz J. Active smoking and the risk of type 2 diabetes: a systematic review and meta-analysis. *JAMA*. 2007; 298(22):2654-2664.
2. Hur NW, Kim HC, Nam CM, Jee SH, Lee HC, Suh I. Smoking cessation and risk of type 2 diabetes mellitus: Korea Medical Insurance Corporation Study. *Eur J Cardiovasc Prev Rehabil*. 2007;14(2):244-249.
3. Wannamethee SG, Shaper AG, Perry IJ; British Regional Heart Study. Smoking as a modifiable risk factor for type 2 diabetes in middle-aged men. *Diabetes Care*. 2001;24(9):1590-1595.
4. Yeh HC, Duncan BB, Schmidt MI, Wang NY, Brancati FL. Smoking, smoking cessation, and risk for type 2 diabetes mellitus: a cohort study. *Ann Intern Med*. 2010;152(1):10-17.
5. Will JC, Galuska DA, Ford ES, Mokdad A, Calle EE. Cigarette smoking and diabetes mellitus: evidence of a positive association from a large prospective cohort study. *Int J Epidemiol*. 2001;30(3):540-546.
6. Zhang LX, Curhan GC, Hu FB, Rimm EB, Forman JP. Association between passive and active smoking and incident type 2 diabetes in women. *Diabetes Care*. 2011;34(4):892-897.
7. The Women's Health Initiative Study Group. Design of the Women's Health Initiative clinical trial and observational study. *Control Clin Trials*. 1998; 19(1):61-109.
8. Margolis KL, Lihong Qi, Brzyski R, et al; Women Health Initiative Investigators. Validity of diabetes self-reports in the Women's Health Initiative: comparison with medication inventories and fasting glucose measurements. *Clin Trials*. 2008;5(3):240-247.
9. Spring B, Howe D, Berendsen M, et al. Behavioral intervention to promote smoking cessation and prevent weight gain: a systematic review and meta-analysis. *Addiction*. 2009;104(9):1472-1486.

Obesity and Increased Risk for Oligozoospermia and Azoospermia

The global obesity epidemic parallels a decrease in male fertility. Yet, the association between body mass index (BMI) and sperm parameters remains controversial. A negative correlation between BMI and sperm concentration or total sperm count was shown by several reports[1,2] but not documented by others.[3,4] The purpose of this report was to update the level of evidence on the association between BMI and sperm count through a systematic review and meta-analysis.

Methods. A systematic review of available literature was conducted to investigate the impact of BMI on sperm count in men according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement. A PubMed and EMBASE search identified relevant studies published until October 2010. Authors of relevant studies were contacted by e-mail and asked to complete a standardized data form regarding total sperm counts according to BMI categories. Unpublished data obtained from patients followed at the Infertility Center of Jean Verdier Hospital, Bondy, France, between January 2007 and December 2010 were also included.

The following BMI categories were used for analyses: lower than 18.5, 18.5 to 24.9, 25.0 to 29.9, and 30.0 or higher (calculated as weight in kilograms divided by height in meters squared). Data were stratified according to total sperm count as having normozoospermia ($\geq 40 \times 10^6$ spermatozoa per ejaculate), oligozoospermia ($< 40 \times 10^6$ but > 0 spermatozoa per ejaculate), and azoospermia (absence of spermatozoa), as specified in World Health Organization guidelines.[5] We performed random effects models to obtain summary estimates to account for interstudy variation. Studies were weighted according to an estimate of statistical size defined as the inverse of the variance of the log odds ratio (OR). Prevalent ORs and 95% confidence intervals are presented. We calculated the ORs of overweight and obese men presenting with oligozoospermia or azoospermia compared with normal-weight men.

Results. A total of 8873 articles were identified. In total, 31 articles were potentially appropriate to be included in the meta-analysis because they investigated the relationship between BMI and sperm parameters. A total of 14 eligible studies were included in the present meta-analysis, corresponding to a total study sample of 9779 individuals. Overweight men were at significantly increased odds of presenting with oligozoospermia (OR, 1.11; 95% CI, 1.01-1.20) or azoospermia (OR, 1.39; 95% CI, 0.98-1.97) compared with normal-weight men (**Figure**). Likewise, obese men were at increased risk of oligozoospermia (OR, 1.42; 95% CI, 1.12-1.79) or azoospermia (OR, 1.81; 95% CI, 1.23-2.66) compared with normal-weight men (Figure).

Comment. This meta-analysis based on 9779 men showed an inverse association between overweight or obesity and abnormal sperm count. This relationship may be explained by different pathophysiological hypotheses: (1) hypogonadotropic hyperestrogenic hypogonadism due to aromatization of steroids in estrogens in peripheral tissues[6]; (2) direct alterations of spermatogenesis and Sertoli cell function[7]; (3) hip, abdominal, and scrotal fat-tissue accumulation leading to the increase of scrotal temperature[8]; and (4) accumulation of toxic substances and liposoluble endocrine disruptors in fatty tissue.[2]

Our strategy based on individual patient data and analysis of dichotomized sperm count made it possible to have a more homogeneous meta-analysis of the available evidence. Limitations of our study are the exclusion of 15 studies because of incomplete data or lack of response from authors and the variations in the study populations. Yet, this variability suggests that our findings may

©2012 American Medical Association. All rights reserved.

Downloaded From: http://jamanetwork.com/ on 05/19/2013

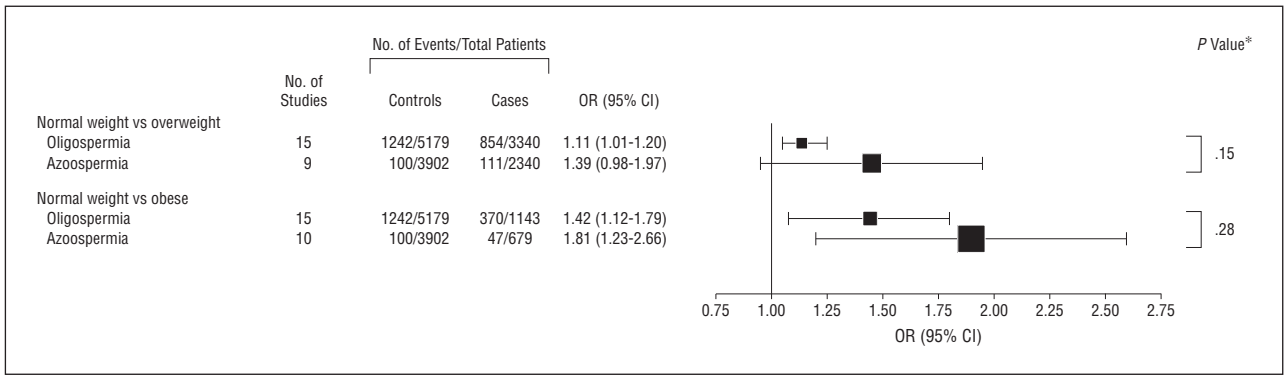

Figure. Association between oligozoospermia and azoospermia stratified by body mass index (BMI) categories. Normal weight: BMI between 18.5 and 24.9 (calculated as weight in kilograms divided by height in meters squared); overweight: BMI between 25.0 and 29.9; obese: BMI greater than 30.0. *P value for heterogeneity. OR indicates odds ratio.

be generalizable to both infertile and general population. We were also reliant on BMI and conventional semen parameters as relevant measures of body fat content and assessment of fertility potential. However, even if they may not be the best indicators, they remain the gold standard for clinical evaluation of adiposity and male fertility, respectively, and allow a clear application of our findings. On the other hand, the strengths of our meta-analysis are a large sample size based on a collection of individual level data.

In conclusion, overweight and obesity are associated with an increased risk of azoospermia or oligozoospermia. These data strongly suggest that excess body weight affects sperm production.

Nathalie Sermondade, MD, MSc
Céline Faure, PhD
Léopold Fezeu, MD, PhD
Rachel Lévy, MD, PhD
Sébastien Czernichow, MD, PhD
and the Obesity-Fertility Collaborative Group

Author Affiliations: Service d'Histologie-Embryologie-Cytogénétique-CECOS, Hôpital Jean Verdier (Assistance Publique–Hôpitaux de Paris [AP-HP]), Bondy, France (Drs Sermondade, Faure, and Lévy); Research Unit on Nutritional Epidemiology, UMR U557 INSERM, U1125 INRA, CNAM, Université Paris 13, Bobigny, France (Drs Sermondade, Faure, Fezeu, and Lévy); and Department of Nutrition, Ambroise Paré Hospital, University of Versailles St Quentin en Yvelines, Boulogne-Billancourt, France, and INSERM, U1018, Centre for Research in Epidemiology and Population Health, Villejuif, France (Dr Czernichow).

Correspondence: Dr Czernichow, Department of Nutrition, Ambroise Paré Hospital (AP-HP), 9 Ave Charles-de-Gaulle, 92100 Boulogne-Billancourt, France (sebastien.czernichow@apr.aphp.fr).

Author Contributions: Drs Sermondade, Fezeu, and Czernichow had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analyses. Drs Lévy and Czernichow contributed equally to the manuscript. *Study concept and design:* Sermondade, Lévy, and Czernichow. *Acquisition of data:* Sermondade. *Analysis and interpretation of data:* Sermondade, Faure, Fezeu, Lévy, and Czernichow. *Drafting of the manuscript:* Sermondade and Czernichow. *Critical revision of the manuscript for important intellectual content:* Sermondade, Faure, Fezeu, and Czernichow. *Statistical analysis:* Fezeu and Czernichow. *Administrative, technical, and material support:* Sermondade, Faure, and Lévy. *Study supervision:* Lévy and Czernichow.

The Obesity-Fertility Collaborative Group: Nathalie Sermondade, MD, MSc, Céline Faure, PhD, Léopold Fezeu, MD, PhD, and Rachel Lévy, MD, PhD (Hôpital Jean Verdier, Bondy, France & Université Paris 13, Bobigny, France); Sébastien Czernichow, MD, PhD (Ambroise Paré Hospital & University of Versailles Saint Quentin en Yvelines, Boulogne-Billancourt, France, and INSERM, U1018, Centre for Research in Epidemiology and Population Health, Villejuif, France); Tina Kold Jensen, MD, PhD (Rigshospitalet, Copenhagen, Denmark); Madelon Van Wely, PhD (Academic Medical Centre, Amsterdam, the Netherlands); Jia Cao, PhD (Third Military Medical University, Chongqing, China); Ana Carolina Martini, PhD (Universidad Nacional de Córdoba, Córdoba, Argentina); Jorge Chavarro, MD, PhD (Brigham and Women's Hospital & Harvard Medical School, Boston, Massachusetts); Sandor Koloszar, MD, PhD (University of Szeged, Szeged, Hungary); Cecilia H. Ramlau-Hansen, MHSc, PhD (Aarhus University, Aarhus C, Denmark); Régine P. M. Steegers-Theunissen, MD, PhD (Erasmus University Medical Center, Rotterdam, the Netherlands); Branko Zorn, MD, PhD (University Medical Center, Ljubljana, Slovenia); Alex J. Polotsky, MD, MSc (University of Colorado Denver, Aurora); Brenda Eskenazi, PhD (UC Berkeley School of Public Health, Berkeley, California); Elin V. Magnusdottir, MSc (University of Iceland, Reykjavik); Imre Fejes, MD, PhD (University of Szeged, Szeged, Hungary); and Serge Hercberg, MD, PhD (Hôpital Avicenne, Bobigny, France & Université Paris 13, Bobigny).

Financial Disclosure: None reported.

Funding/Support: Dr Chavarro was supported in part by National Institute of Diabetes and Digestive and Kidney Diseases grant 5P30DK046200-19 and Dr Eskenazi was supported in part by National Institutes of Health grant P42ES04705.

Additional Contributions: The following individuals or departments performed the data collection in each of their centers: Niels Jorgensen, Rigshospitalet, Copenhagen,

©2012 American Medical Association. All rights reserved.

Downloaded From: http://jamanetwork.com/ on 05/19/2013

Denmark; Yafei Li, Third Military Medical University, Chongqing, China; Zhihong Cui, Third Military Medical University, Chongqing, China; Rosa Molina, Laboratorio de Andrologia y Reproduccion, Córdoba, Argentina; Ruben Daniel Ruiz, Facultad de Ciencias Medicas, Universidad Nacional de Córdoba, Córdoba, Argentina; Thomas L. Toth, Harvard Medical School, Boston, Massachusetts; Russ Hauser, Harvard School of Public Health, Boston; Janos Szollosi, University of Szeged, Szeged, Hungary; Ane Marie Thulstrup, Aarhus University Hospital, Aarhus, Denmark; Joop Laven, Marijana Vujkovic, and Fatima Hammiche, Erasmus University Medical Center, Rotterdam, the Netherlands; Gregor Majdic, Center for Animal Genomics, Veterinary Faculty, University of Ljubljana, Ljubljana, Slovenia; Rosana Hernandez Weldon, UC Berkeley School of Public Health, Berkeley, California; Andrew J. Wyrobek, Lawrence Berkeley National Laboratory, Berkeley; Department of Assisted Reproduction, Landspitali University Hospital, Landspitali, Iceland; and Zoltan Zavaczki, Landstinget Gavleborg, Hudiksvall, Sweden.

1. Hammoud AO, Wilde N, Gibson M, Parks A, Carrell DT, Meikle AW. Male obesity and alteration in sperm parameters. *Fertil Steril*. 2008;90(6):2222-2225.
2. Magnusdottir EV, Thorsteinsson T, Thorsteinsdottir S, Heimisdottir M, Olafsdottir K. Persistent organochlorines, sedentary occupation, obesity and human male subfertility. *Hum Reprod*. 2005;20(1):208-215.
3. Chavarro JE, Toth TL, Wright DL, Meeker JD, Hauser R. Body mass index in relation to semen quality, sperm DNA integrity, and serum reproductive hormone levels among men attending an infertility clinic. *Fertil Steril*. 2010; 93(7):2222-2231.
4. Jensen TK, Andersson AM, Jørgensen N, et al. Body mass index in relation to semen quality and reproductive hormones among 1,558 Danish men. *Fertil Steril*. 2004;82(4):863-870.
5. Cooper TG, Noonan E, von Eckardstein S, et al. World Health Organization reference values for human semen characteristics. *Hum Reprod Update*. 2010; 16(3):231-245.
6. Schneider G, Kirschner MA, Berkowitz R, Ertel NH. Increased estrogen production in obese men. *J Clin Endocrinol Metab*. 1979;48(4):633-638.
7. Winters SJ, Wang C, Abdelrahaman E, Hadeed V, Dyky MA, Brufsky A. Inhibin-B levels in healthy young adult men and prepubertal boys: is obesity the cause for the contemporary decline in sperm count because of fewer Sertoli cells? *J Androl*. 2006;27(4):560-564.
8. Shafik A, Olfat S. Scrotal lipomatosis. *Br J Urol*. 1981;53(1):50-54.

Effect of Antihypertensive Therapy on Cognitive Function in Early Executive Cognitive Impairment: A Double-blind Randomized Clinical Trial

Approximately 50% of older hypertensive individuals have difficulties in executive function, the cognitive domain that controls complex tasks.[1] Hypertensive individuals with executive dysfunction have a high rate of conversion to dementia.[2] To our knowledge, to date, no study has investigated therapeutic options for executive dysfunction. Recent evidence suggests that the renin angiotensin system plays a central role in linking hypertension to cognitive function, offering new therapeutic options for cognitive protection.[3] In the brain, angiotensin receptor blockers (ARBs) block the type 1 but not the type 2 receptor, whereas angiotensin-converting enzyme inhibitors (ACEIs) decrease activation of both receptors. Activating the type 2 receptor may provide cognitive protection.[4] We therefore hypothesized that an ARB-based regimen would be superior to other antihypertensive regimens in cognitive protection, especially executive function, and conducted a 12-month double-blind randomized clinical trial comparing candesartan, lisinopril, and hydrochlorothiazide in hypertensive individuals with early executive dysfunction.

Methods. The study design is fully described elsewhere.[5] Subjects were recruited from the greater Boston area, Massachusetts, and were 60 years or older, had hypertension (systolic blood pressure >140 mm Hg and diastolic blood pressure >90 mm Hg), and demonstrated evidence of executive dysfunction based on the executive clock draw test (CLOX1 score <10). We excluded those with a Mini-Mental State Examination (MMSE) score lower than 20 or those with a clinical diagnosis of dementia, diabetes mellitus, stroke, or congestive heart failure. Antihypertensive medications were tapered using a standard protocol described elsewhere.[5] Randomization using a computer-generated random allocation sequence occurred after baseline data collection, and participants were seen every 2 weeks until their blood pressure was controlled (<140/90 mm Hg). Participants were treated with escalating doses of lisinopril, candesartan, or hydrochlorothiazide to achieve a blood pressure lower than 140/90 mm Hg. Long-acting nifedipine and long-acting metoprolol succinate were added if the goal blood pressure was not achieved. Cognitive assessments were repeated at 6 and 12 months and included Trail-Making Test (TMT) parts A and B, which assesses executive function; Hopkins Verbal Learning Test–Revised (HVLT), which assesses memory; and the Digit Span Test, which assesses attention. The Hebrew SeniorLife institutional review board approved the study, and written informed consent was obtained. An intention-to-treat analysis was performed, and linear mixed models for repeated measures were used to compare the progression of cognitive outcomes in the 3 groups. Least-square means adjusted for age and baseline MMSE score were computed for each visit by treatment group.

Results. Of the 63 eligible individuals screened, 53 stopped their antihypertensive medications and were randomized to lisinopril (n=18), candesartan (n=20), or hydrochlorothiazide (n=15); 47 completed 6 months, and 31 completed 12 months. A sample description is provided in the eTable (http://www.archinternmed.com). The number of subjects achieving blood pressure control were similar (lisinopril, 91%; candesartan, 100%; and hydrochlorothiazide, 100%; $P=.40$) and systolic blood pressure reductions were similar in all 3 groups (mean [SD] reduction was 28 [5] mm Hg for lisinopril, 27 [5] mm Hg for candesartan, and 21 [5] mm Hg for hydrochlorothiazide; $P=.75$). There were no differences in the reported adverse events between the 3 groups. After adjusting for age and baseline MMSE score, those randomized to candesartan demonstrated the greatest improvement in TMT part B ($P=.008$); the adjusted TMT (parts A and B), which adjusts the test for motor speed ($P=.01$); and the recognition portion of the HVLT ($P=.03$) (**Figure**).

Comment. This study suggests that ARBs are associated with improvement in executive function in older hypertensive adults with early executive cognitive impair-

©2012 American Medical Association. All rights reserved.

Downloaded From: http://jamanetwork.com/ on 05/19/2013