Interaction between postmenopausal hormone therapy and diabetes on cataract

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Abstract

Objective: We investigated whether postmenopausal hormone therapy (HT) use interacts with diabetes, a risk factor for several age-related eye diseases.

Methods: A cross-sectional analysis of women involved in the Canadian Longitudinal Study on Aging was performed. The random sample comprised of 15,320 community-dwelling women between ages 45 and 85 years old sampled from areas adjacent to 11 data collection centers across Canada. Information on menopausal status and HT were collected by self-report. Data on diabetes and eye disease were obtained by self-report of a physician diagnosis. Multivariable logistic regression was used.

Results: After adjusting for demographic, lifestyle, and health variables, a multiplicative interaction was identified such that HT use for 10 years or more was associated with a much higher odds of a report of cataract (odds ratio = 2.44, 95% confidence interval 1.49, 3.99) but not in long-term HT users with no diabetes (odds ratio = 1.03, 95% confidence interval 0.87, 1.21) (interaction term P value = 0.013). HT use was not associated with glaucoma or macular degeneration.

Conclusions: Long-term HT use and type 2 diabetes interact in their relationship with cataract. This novel finding should be confirmed. If confirmed, women with type 2 diabetes should be informed that long-term HT use increases their risk of cataract.

Key Words: Cataract – Canadian Longitudinal Study on Aging – Diabetes – Glaucoma – Hormone therapy.

Video Summary: http://links.lww.com/MENO/A519.

Much research has been done on whether there is a relationship between postmenopausal hormone therapy (HT) and age-related eye disease but little consensus exists. Several studies found a protective association between HT use and cataract.1-4 Some studies, particularly more recent and longitudinal ones, have, however, found either no association or a harmful association between HT use and cataract or cataract surgery.5-9 A lack of consensus also exists for age-related macular degeneration with some studies finding a protective effect of HT use while others report no association.10-12 Similarly, several studies have reported a protective association between HT use and glaucoma or intraocular pressure13-16 but not all12 or only in certain subgroups.17

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The frequency of use and reasons for taking HT have changed over the last 20 years since the publication of the principal results from the Women’s Health Initiative trial in 2002. That trial found that HT use could increase a woman’s risk of certain cancers, heart disease, and stroke, but that HT could be used safely for the short-term relief of menopausal symptoms. Prescriptions for HT decreased sharply upon the publication of these results. Many reasons could exist regarding why results on the relationship between HT and age-related eye disease are so inconsistent. One reason could be due to undetected interaction in prior studies. Our hypothesis was that HT may act differently in the eye depending on the presence of diabetes, a consistent risk factor for cataract and glaucoma and an inconsistent risk factor for age-related macular degeneration, and which has increased in prevalence over the last 20 years. Most studies are not large enough to have the statistical power to examine interaction. The Canadian Longitudinal Study on Aging is a large, national study of 15,320 women that has sufficient power to examine the interaction between HT and diabetes.

**METHODS**

**Study design and sample**

Baseline data from the Comprehensive Cohort of the Canadian Longitudinal Study on Aging (CLSA), which include 15,320 community-dwelling women aged 45 to 85 years, were used for this analysis. Exclusion criteria included living in an institution or on a First Nations reserve or settlement, being a full-time member of the Canadian Armed Forces, being unable to speak French or English, and having overt cognitive impairment (unable to understand the study or answer basic questions about themselves). The Comprehensive Cohort participants underwent both a home interview and a face-to-face interview and exam at 1 of 11 Data Collection Sites (DCS) between 2012 and 2015.

The comprehensive cohort participants represent a random sample of community-dwelling adults within a 25 to 50 km radius of 1 of the 11 DCS (Victoria, Vancouver, Surrey, Calgary, Winnipeg, Hamilton, Ottawa, Montreal, Sherbrooke, Halifax, St. John’s) in 7 Canadian provinces recruited from either provincial health databases or random digit dialing. Each randomly chosen eligible person recruited from a provincial health registry was sent a consent form to sign and return. For those recruited through random digit dialing, a random sample of landline telephone numbers was selected for a given geographic area. Once a call was answered, eligibility was established, and consent was obtained. Stratified sampling was used to ensure adequate representation of various demographic groups. Strata within a province were defined according to age group, sex, and distance from the DCS. Sampling weights were developed to ensure generalizability of the samples and to control for nonresponse bias. Research ethics boards in seven provinces approved the CLSA project. In addition, the Research Ethics Board of the Ottawa Hospital Research Network approved this specific work. Research followed the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants. The CLSA study design and methods have been previously described by Raina et al elsewhere.

**Age-related eye disease**

Participants were asked if they had ever been told by a doctor that they had the following eye diseases: cataract, glaucoma, or macular degeneration. Cataract, glaucoma, and macular degeneration were deemed present if a participant answered ‘‘yes’’ to the former question.

**Menopause and postmenopausal hormone therapy variables**

Menopausal status was assessed by the following question: ‘‘Have you gone through menopause, meaning that your menstrual periods stopped for at least one year and did not restart?’’ Women who answered ‘‘yes’’ were classified as naturally postmenopausal. Individual age at natural menopause was reported in response to the following question: ‘‘How old were you when your menstrual periods stopped for at least one year and did not re-start?’’ Answers were recorded as age in years. Age at natural menopause and menopause type were computed into a new categorical variable that encompassed the following groups: women with premature menopause (menopause occurred <40 y), early natural menopause (menopause occurred naturally between ages 40 and 44 y), normal natural menopause (menopause occurred naturally between ages 45 and 54 y), late natural menopause (menopause occurred naturally ≥55 y), and those who reported hysterectomy. To avoid small numbers, categories for premature menopause and early natural menopause were collapsed and labeled as having early natural menopause.

Ever use of postmenopausal HT was captured by the following question: ‘‘Have you ever used any hormone replacement therapy, sometimes called HRT, for any reason?’’ A new HT use variable was created using the following variables: age at the time of interview, duration of HT use, and age at initiation of HT. Women using HT when interviewed were defined as current users, women who had used HT in the past were labeled as past users, whereas those who had never taken HT were labeled as never users. Duration of HT use was categorized as never, less than 10, or 10 years or more. This cut off was chosen because it gives a fairly equal distribution among the different categories.

**Covariates**

Sociodemographic variables included age at time of interview, province of residence, and ethnicity classified as white versus non-white, where non-white included Aboriginal, South Asian, Chinese, Hispanic, Arab, and Black individuals. Additional sociodemographic information included the self-report of the highest education level, marital status, and annual household income in Canadian dollars. Participants were asked whether they had ever smoked at least 100 cigarettes and if they still smoked. Participants reported
whether a doctor had diagnosed them with diabetes, borderline diabetes, or high blood sugar. Those who answered affirmatively were asked the type of diabetes with choices being type 1, type 2, or neither. Participants were asked if they had ever been diagnosed with hypertension or high blood pressure. Seated, resting blood pressure was also measured using a random-zero sphygmomanometer; the average of the last two out of three readings was used. Hypertension was defined as self-reported diagnosis of hypertension, or a systolic blood pressure greater than 140 mm Hg or diastolic blood pressure greater than 90 mm Hg. Height and weight were measured and used to calculate body mass index in kg/m².

Statistical analyses

Our primary outcome was cataract given the majority of HT research is with this outcome. Glaucoma and macular degeneration were secondary outcomes. Characteristics are presented as percentages for categorical variables and mean ± SE for continuous variables. Because age is a major risk factor for all outcome variables, age-adjusted logistic regression analyses were first done to examine relationships between HT use and each outcome. Multiple logistic regression was then used to analyze the association between HT use and each outcome. Interaction was assessed in two ways: by stratification to qualitatively assess homogeneity of effects and, if present, by the inclusion of an interaction term to test for statistical significance. Odds ratios (OR) and 95% confidence intervals (CIs) were presented. Statistical significance for all analyses was defined as \( P < 0.05 \). All analyses were conducted using Stata version 15.0 (StataCorp, College Station, TX). Sample weight and strata information that account for the complex study design were used.

Sensitivity analyses were done excluding the following groups to determine whether the results changed: (1) women with a previous diagnosis of breast, ovarian, or endometrial cancers \( (n = 1,180) \), these conditions can mask the true age at menopause; (2) women who used HT before the reported onset of menopause \( (n = 740) \), HT can mask the true age at menopause; (3) women who reported an age of more than 62 years \( (n = 72) \) at natural menopause, these values may be erroneous.

RESULTS

Some women were excluded from the analysis. Premenopausal women were excluded from the analysis since we were focusing on postmenopausal HT use \( (n = 2,557) \). Women who did not know or refused to report if they had undergone menopause \( (<1\%, \; n = 103) \) were also excluded. After these exclusions, 12,660 women remained for analysis. Women are compared by their use of HT in Table 1. There were 186 (1.5%) women who did not report data on HT use. Long-term users of HT were older than nonusers. Other large differences were that long-term HT users were more likely to be white, to be living with a partner, to have lower education and household income, to have surgical or early menopause, to have visited the doctor in the last year, and to report high blood pressure.

Women are compared by their self-report of a diagnosis of cataract in Table 2. Women with a report of cataract were older than those without. Other large differences included that women living with a partner, with less education and household income, who had late or surgical menopause, who visited a doctor in the last year, or who had high blood pressure or type 1 or 2 diabetes were more likely to report cataract.

After age adjustment, HT duration was associated with a report of cataract with women who used HT for less than 10 years \( (OR = 1.18, \; 95\% \; CI = 1.05, \; 1.32) \) and having used HT for 10 years or more \( (OR = 1.16, \; 95\% \; CI = 1.01, \; 1.32) \) being statistically significantly more likely to report cataract than never HT users. Also, women who were past HT users were 1.20 times statistically significantly more likely to report cataract \( (95\% \; CI = 1.07-1.34) \) while current use was not associated. Women with a surgical menopause were more
likely to report having cataract (OR = 1.17, 95% CI = 1.03, 1.34) compared to women with a natural menopause between ages 45 and 54 years.

The multivariable-adjusted associations between HT duration, menopausal age and type, and cataract are presented in Table 3. Women who used HT for less than 10 years had a significantly greater odds of cataract (OR = 1.23, 95% CI = 1.09, 1.38) compared to women who never used HT, whereas those who used for 10 or more years had a borderline association (OR = 1.15, 95% CI 0.99, 1.33). Surgical menopause was not associated with cataract after full adjustment. Other variables statistically significantly associated with cataract were older age, non-white ethnicity, not living with a partner, former smoking, type 1 diabetes, type 2 diabetes, diabetes that is neither type 1 or type 2, and body mass index ($P < 0.05$).

A multiplicative interaction was identified (Table 4, Fig. 1) such that HT duration of 10 or more years was associated with a much higher odds of a report of cataract in women with type 2 diabetes (OR = 2.44, 95% CI 1.49, 3.99) but not in women without diabetes (OR = 1.03, 95% CI 0.87, 1.21) (interaction term $P$ value = 0.013). There was no interaction for use less than 10 years as both ORs in those with and without type 2 diabetes were around 1.2. There was no interaction with diabetes that was neither type 1 nor type 2 and we did not have adequate numbers of people with type 1 diabetes (n = 66) to examine interaction specifically in that group.

In addition to HT duration, both past (OR = 1.18, 95% CI 1.06, 1.33) and current use of HT (OR = 1.23, 95% CI 1.01, 1.50) were associated with cataract after multivariable

### Table 2. Comparison of women by report of cataract

| Age, per 1 y | n = 4,658 | n = 7,767 | Report of cataract | Report of cataract |
|-------------|-----------|-----------|--------------------|--------------------|
| 59.7 (0.1)  | 70.6 (0.1)| Body mass index, kg/m² 27.7 (0.1) 28.1 (0.1)

### Table 3. Multiple regression analysis of hormone therapy, menopausal age and type, and cataract

| HT duration | Number of cases | Report of cataract adjusted odds ratio | 95% CI |
|-------------|----------------|---------------------------------------|-------|
| Never       | 2,225          | 1.00                                  | Reference |
| <10 y       | 1,301          | 1.23                                  | 1.09, 1.38 |
| ≥10 y       | 1,028          | 1.15                                  | 0.99, 1.33 |

### Table 4. Stratified analysis of hormone therapy and cataract by type 2 diabetes status

| Strata | Number of cases | HT duration | Report of cataract OR* | 95% CI |
|--------|----------------|-------------|------------------------|-------|
| No diabetes | n = 10,137  | Never | 1.00 | Reference |
|          | 1,038         | <10 y | 1.21 | 1.07, 1.39 |
|          | 806           | ≥10 y | 1.03 | 0.87, 1.21 |

*Adjusted for all variables in table in addition to education, household income, visit to a doctor in the last year, high blood pressure, and province.

**Interaction term P value for type 2 diabetes and HT duration ≥10 Years = 0.013.**
adjustment. No interactions with diabetes were, however, found. There were no statistically significant associations between HT duration or HT use with our secondary outcomes: glaucoma and macular degeneration. HT use for less than 10 years (OR = 1.05, 95% CI 0.85, 1.30) and HT use of 10 years or more (OR = 1.07, 95% CI 0.83, 1.37) were not associated with glaucoma. HT use of less than 10 years (OR = 1.20, 95% CI 0.96, 1.50) and HT use of 10 years or more (OR = 1.01, 95% CI 0.79, 1.30) were also not significantly associated with macular degeneration. No interactions were detected.

In sensitivity analyses, results were essentially the same after the exclusion of women with breast, endometrial, and ovarian cancers (n = 1,180), who reported using HT before the onset of menopause (n = 740), or who reported implausible ages at natural menopause (n = 72).

DISCUSSION

In this large, representative sample of Canadian women, HT use in general was weakly associated with the report of cataract. This is, however, the first article to report an interaction between long-term HT use and type 2 diabetes in their relationship with cataract. Long-term HT users with type 2 diabetes had a 2.44-fold higher odds of reporting cataract than those who never used HT but had type 2 diabetes. This finding is important because results from the Women’s Health Initiative trial and others have indicated that HT use could reduce the risk of developing type 2 diabetes. One possible mechanism could be through inflammatory factors such as C-reactive protein. Some studies have found that both HT use and type 2 diabetes can increase levels of inflammatory factors such as C-reactive protein, which may be related to cataract.

Although most prior studies have found HT use to be related to a lower odds of cataract, a few have reported findings similar to ours that HT use is related to a higher odds of cataract extraction after multivariable adjustment. Ever using HT was also associated with cataract extraction in the Age-Related Eye Disease Study cohort study (hazard ratio = 1.22, 95% CI 1.04, 1.43). In a cohort of 14,337 Chinese women, Tian et al also found that women who had ever used HT had a higher odds of having cataract (OR = 1.61, 95% CI 1.05, 2.47).

A strength of this research is the use of a large, representative, population-based sample of women from across Canada, which allowed us to have adequate statistical power to detect modestly sized interaction ORs. Another strength is the abundant data available to adjust for confounding. There are some limitations to our research, however. First, eye disease was self-reported rather than ascertained through an ophthalmological examination. Second, information on HT and menopause were collected by self-report and we did not have information on the type of HT, the delivery mode of HT, age of menarche, or prior oral contraception use. HT preparations can vary in their use of estrogen, progestin, and selective estrogen receptor modulators. Furthermore, there are different types of estrogens and progestins used in HT preparations. It is unknown why HT use could be harmful to the lens, especially in those with type 2 diabetes. Estrogen and progesterone receptors are present throughout the eye. One possible mechanism could be through inflammatory factors such as C-reactive protein. Some studies have found that both HT use and type 2 diabetes can increase levels of inflammatory factors such as C-reactive protein, which may be related to cataract.
progestins in the various preparations which may lead to different potencies and mechanisms of action. These different preparations may have varying effects on the eye.14,38 Prior associations between oral contraception use and glaucoma39 and cataract40 have been reported, although null findings have been reported as well.41 Third, the cross-sectional nature of the study does not allow us to disentangle the temporality of HT use, type 2 diabetes, and the onset of eye disease.

**CONCLUSION**

In conclusion, our results indicated that women who are long-term users of HT with type 2 diabetes had a 2.44 higher odds of cataract than women who never used HT with type 2 diabetes. These findings should be confirmed by prospective studies with longitudinal data on diabetes, HT use, and cataract. If confirmed, women with type 2 diabetes taking HT for 10 or more years should be counseled that they may be at a higher risk of cataract.

**REFERENCES**

1. Lai K, Cui J, Ni S, Zhang Y, He J, Yao K. The effects of postmenopausal hormone use on cataract: a meta-analysis. *PLoS One* 2013;8:e78647.
2. Klein BE, Klein R, Ritter LL. Is there evidence of an estrogen effect on age-related lens opacities? The Beaver Dam Eye Study. *Arch Ophthalmol* 1994;112:85-91.
3. Worzala K, Hiller R, Sperduto RD, et al. Postmenopausal estrogen use, type of menopause, and lens opacities: the Framingham studies. *Arch Intern Med* 2001;161:1448-1454.
4. Freeman EE, Munoz B, Schein OD, West SK. Hormone replacement therapy and lens opacities: the Salisbury Eye Evaluation project. *Arch Ophthalmol* 2001;119:1673-1692.
5. Lindblad BE, Håkansson N, Philipson B, Wolk A. Hormone replacement therapy in relation to risk of cataract extraction. A prospective study of women. *Ophthalmology* 2010;117:424-430.
6. Tian Y, Wu J, Xu G, et al. Parity and the risk of cataract: a cross-sectional analysis in the Dongfeng-Tongji cohort study. *Br J Ophthalmol* 2015;99:1650-1654.
7. Kanthan GL, Wang JJ, Burlutsky G, Rochondina E, Cumming RG, Mitchell P. Exogenous oestrogen exposure, female reproductive factors and the long-term incidence of cataract: the Blue Mountains Eye Study. *Acta Ophthalmol* 2010;58:773-778.
8. Freeman EE, Munoz B, Schein OD, West SK. Incidence and progression of lens opacities: effect of hormone replacement therapy and reproductive factors. *Epidemiology* 2004;15:451-457.
9. Floud S, Kuper H, Reeves GK, Beral V, Green J. Risk factors for cataracts treated surgically in postmenopausal women. *Ophthalmology* 2016;123:1704-1710.
10. Freeman EE, Munoz B, Bressler SB, West SK. Hormone replacement therapy, reproductive factors, and age-related macular degeneration: the Salisbury Eye Evaluation Project. *Ophthalmic Epidemiol* 2005;12:37-45.
11. Feskancih D, Cho E, Schaumberg DA, Colditz GA, Hankinson SE. Menopausal and reproductive factors and risk of age-related macular degeneration. *Arch Ophthalmol* 2008;126:519-524.
12. Lam JSH, Tay WT, Aung T, Saw SM, Wong TY. Female reproductive factors and major eye diseases in Asian women—the Singapore Malay Eye Study. *Ophthalmic Epidemiol* 2014;21:92-98.
13. Newman-Casey PA, Talwar N, Nan B, Musch DC, Pasquale LR, Stein JD. The potential association between postmenopausal hormone use and primary open-angle glaucoma. *JAMA Ophthalmol* 2014;132:298-303.
14. Pasquale LR, Rosner BA, Hankinson SE, Kang JH. Attributes of female reproductive aging and their relation to primary open-angle glaucoma: a prospective study. *J Glaucoma* 2007;16:598-605.
15. Vajaranant TS, Maki PM, Pasquale LR, Lee A, Kim H, Haan MN. Effects of hormone therapy on intraocular pressure: the Women’s Health Initiative—Eye Study. *Am J Ophthalmol* 2016;155:11-124.
16. Dwundura SS, Wiggs JL, Sullivan DA, Pasquale LR. Is estrogen a therapeutic target for glaucoma? *Semim Ophthalmol* 2016;31:140-146.
17. Vajaranant TS, Ray RM, Pasquale LR, et al. Racial differences in the effects of hormone therapy on incident open-angle glaucoma in a randomized trial. *Am J Ophthalmol* 2018;175:110-120.
18. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women’s Health Initiative randomized controlled trial. *JAMA* 2002;288:321-333.
19. Hing E, Brett KM. Changes in U.S. prescribing patterns of menopausal hormone therapy, 2001-2003. *Obset Gynecol* 2006;108:33-40.
20. Menke A, Casagrande S, Geiss L, Cowie CC. Prevalence of and trends in diabetes among adults in the United States, 1988-2012. *JAMA* 2015;314:1021-1029.
21. Raina PS, Wolfrom C, Kirkland SA, et al. The Canadian longitudinal study on aging (CLSA). *Can J Aging* 2009;28:221-229.
22. WHO. Research on the Menopause: Report of a WHO Scientific Working Group. 1981: 8. Available at: http://apps.who.int/iris/handle/10665/41526. Accessed July 10, 2019.
23. Chang JH, Koo E, Agron E, et al. Risk factors associated with incident cataracts and cataract surgery in the Age-related Eye Disease Study (AREDS). *Ophthalmology* 2011;118:2113-2119.
24. Coleman AL, Miglior S. Risk factors for glaucoma onset and progression. *Surv Ophthalmol* 2008;53(suppl):S3-S10.
25. Chakravartih U, Wong TY, Fretter A, et al. Clinical risk factors for age-related macular degeneration: a systematic review and meta-analysis. *BMC Ophthalmol* 2010;11:31.
26. Clemons TE, Milton RC, Klein R, Ferris FL 3rd. Risk factors for the incidence of advanced age-related macular degeneration in the Age-Related Eye Disease Study (AREDS). AREDS report number 32. *Ophthalmology* 2005;112:533-539.
27. West SK, Valmdrid CT. Epidemiology of risk factors for age-related cataract. *Surv Ophthalmol* 1995:39:323-334.
28. Margolis KL, Bonds DE, Rodabough RJ, et al. Effect of oestrogen plus progestin on the incidence of diabetes in postmenopausal women: results from the Women’s Health Initiative Hormone Trial. *Diabetes Care* 2004;7:1175-1187.
29. Espeland MA, Hogan PE, Fineberg SE, et al. Effect of postmenopausal hormone therapy on glucose and insulin concentrations. *PEPI Investigators. Postmenopausal Estrogen/Progestin Interventions. Diabetes Care* 1998;21:1589-1595.
30. Owsley C, McGwin G Jr, Sloane M, Wells J, Stalvey BT, Gauthreaux S. Impact of cataract surgery on motor vehicle crash involvement by older adults. *JAMA* 2002;288:841-849.
31. Freeman EE, Gressett J, Djafari F, et al. Cataract-related vision loss and depression in a cohort of patients awaiting cataract surgery. *Can J Ophthalmol* 2009;44:171-176.
32. Gupta PD, Johar K, Nagral K, Vasanvada AR. Sex hormone receptors in the human eye. *Surv Ophthalmol* 2005;50:274-284.
33. Wickham LA, Gao J, Toda I, Rocha EM, Ono M, Sullivan DA. Identification of androgen, estrogen and progesterone receptor mRNAs in the human eye. *Surv Ophthalmol* 2006;51:146-153.
34. Cushman M, Legault C, Barrett-Connor E, et al. Effect of postmenopausal hormones on inflammation-sensitive proteins: the Postmenopausal Estrogen/Progestin Interventions (PEPI) Study. *Circulation* 1999;100:717-722.
35. Ridker PM, Hennekens CH, Rifai N, Buring JE, Manson JE. Hormone replacement therapy and increased plasma concentration of C-reactive protein. *Circulation* 1999;100:713-716.
36. Cheng L, Zhuang H, Yang S, Jiang H, Wang S, Zhang J. Exposing the causal effect of C-reactive protein on the risk of type 2 diabetes mellitus: a Mendelian randomization study. *Front Genet* 2018;9:657.
37. Schaumberg DA, Ridker PM, Glynn RJ, Christen WG, Dana MR, Hennekens CH. High levels of plasma C-reactive protein and future risk of age-related cataract. *Ann Epidemiol* 1999;9:166-171.
38. Schaumberg DA, Buring JE, Sullivan DA, Dana MR. Hormone replacement therapy and dry eye syndrome. *JAMA* 2001;286:2114-2119.
39. Wang YE, Kakigi C, Barbosa D, et al. Oral contraceptive use and prevalence of self-reported glaucoma or ocular hypertension in the United States. *Ophthalmology* 2016;123:729-736.
40. Klein BE. Lens opacities in women in Beaver Dam, Wisconsin: is there evidence of an effect of sex hormones? *Trans Am Ophthalmol Soc* 1993;91:517-544.
41. Cumming RG, Mitchell P. Hormone replacement therapy, reproductive factors, and cataract. The Blue Mountains Eye Study. *Am J Epidemiol* 1997;145:242-249.

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