

# Oral estrogen therapy in postmenopausal women is associated with loss of kidney function

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Women are generally protected against progressive loss of kidney function; however, this advantage seems to diminish with menopause. Because of conflicting reports on the association between use of hormone therapy and kidney function we studied 5845 women (1459 on hormone therapy and 4386 non-users) who were over 66 years of age and had at least 2 serum creatinine measurements during the 2 year study period. After adjustment for covariates, hormone use (estrogen-only, progestin-only, or both) was associated with a significant loss of estimated GFR as the primary outcome along with an increased risk of rapid loss of kidney function as the secondary outcome compared to non-users. This increased rate of loss was associated with oral but not transvaginal estrogen use. An increased cumulative dose of estrogen was also associated with a greater decline in estimated GFR. Our study shows an independent association in a dose-dependent manner of estrogen use and loss of kidney function in this elderly population.

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The female gender is protective with respect to loss of kidney function,<sup>1–5</sup> although this advantage may diminish and possibly disappear with the onset of menopause,<sup>6</sup> suggesting a relationship between hormonal status and initiation or progression of renal impairment.

Hormone therapy (HT), estrogen with or without progestin, is a common medication used by women to treat symptoms of menopause and prevent chronic conditions such as osteoporosis.<sup>7</sup> Although treatment of menopausal symptoms is a common indication for short-term use,<sup>8,9</sup> the effects of HT on long-term health outcomes have become increasingly important, particularly since the Women's Health Initiative<sup>10–12</sup> and Heart and Estrogen/Progestin Replacement Study did not find HT to be beneficial.<sup>13</sup> In addition, it is unclear to what extent these results might be extrapolated to other HT regimens that differ in terms of dose, composition, and route of administration.<sup>14</sup>

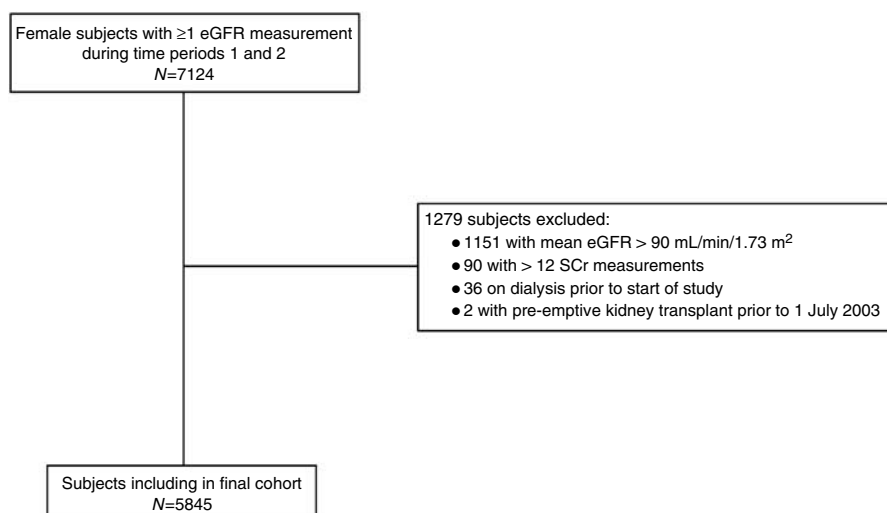
Reports on the association between use of HT and kidney function are conflicting, and there are no studies examining the loss of kidney function as the primary outcome. A small study described an improvement in creatinine clearance over a 3.5-month period after initiation of HT,<sup>15</sup> and a larger case-control study reported a greater creatinine clearance in patients using HT compared with non-users.<sup>16</sup> In contrast, another study reported no change in estimated glomerular filtration rate (eGFR) in association with HT use over a 5-year period.<sup>17</sup> These studies are limited by the fact that they only included subjects from select populations<sup>15–17</sup> or did not account for the type of HT (that is, estrogen or progestin), cumulative dose, or route of delivery.<sup>16,17</sup> Moreover, there were very few elderly subjects included in all three studies. The high prevalence of reduced kidney function in the elderly,<sup>5</sup> coupled with the uncertainty of the effects of HT on kidney function, prompted our examination of the relationship between estrogen and/or progestin use and change in eGFR in a cohort of elderly, community-dwelling women. In addition, we sought to determine whether route of administration or cumulative dose of HT was associated with a change in renal function.

## RESULTS

There were 7124 subjects  $\geq 66$  years of age identified who had at least one outpatient measurement of serum creatinine

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**Figure 1 | Formation of study cohort and criteria for exclusion.**

**Table 1 | Baseline subject characteristics by categorical HT use (n=5845)<sup>a</sup>**

Characteristic	No use (n=4386)	Estrogen only (n=1083)	Progestin only (n=40)	Both (n=336)	P-value <sup>b</sup>
Age (years)	77.5 ± 7.2	75.1 ± 6.1	74.4 ± 5.5	72.8 ± 5.2	<0.0001
eGFR (ml/min/1.73 m <sup>2</sup> )	62.3 ± 17.1	65.4 ± 15.4	63.0 ± 16.0	67.6 ± 15.4	<0.0001
Diabetes (%)	16.6	10.6	22.5	8.6	<0.0001
Chronic disease score	2458 (1789, 3447)	2621 (1853, 3556)	2471 (1868, 3589)	2217 (1555, 3050)	0.0001
<i>Drug use in prior year (%)</i>					
ACE-I/ARB	41.9	40.7	45.0	36.3	0.2
β-Blocker	20.8	24.8	35.0	19.9	0.005
Lipid-lowering	21.1	23.0	35.0	21.7	0.10
Diuretics	41.7	46.8	52.5	36.0	0.0008
NSAIDs	35.8	45.3	35.0	37.8	<0.0001

ACE-I, angiotensin-converting enzyme inhibitor; ANOVA, analysis of variance; ARB, angiotensin-receptor blocker; eGFR, estimated glomerular filtration rate; HT, hormone therapy; NSAID, non-steroidal anti-inflammatory drug.

<sup>a</sup>Age and eGFR expressed as mean ± s.d.; Chronic Disease Score expressed as median and interquartile range.

<sup>b</sup>P-value calculated by ANOVA for age and eGFR,  $\chi^2$ -test for categorical variables, and Kruskal-Wallis test for Chronic Disease Score.

in each of the two defined study periods. As outlined in Figure 1, a total of 1279 subjects were excluded, as they did not meet the inclusion criteria, for a final study cohort of 5845 subjects.

Baseline subject characteristics by type of HT use are shown in Table 1. HT users tended to be younger, less likely to have diabetes, and have a higher baseline eGFR compared with non-users. There were no differences in angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker, lipid-lowering agent, or diuretic use between the groups, although HT users were more likely to be prescribed β-blockers and non-steroidal anti-inflammatory drugs. Estrogens were more commonly used compared with progestins, either as a single agent or as combination therapy.

A total of 5845 subjects, 4386 non-users and 1459 HT users, were followed for a median (interquartile range) of 2 (1.9–2.2) years. After adjustment for age, diabetes, comorbidity, and baseline eGFR, mean eGFR declined by 1.57 ml/min/1.73 m<sup>2</sup> for HT non-users over the study period.

Compared with non-users, and after adjustment for the same covariates, HT use was associated with additional decline in mean eGFR of 1.24 ml/min/1.73 m<sup>2</sup> (95% confidence interval (CI) 0.40–2.08;  $P=0.004$ ) over the study period. HT use was also associated with a 19% increased risk of rapid loss of kidney function (odds ratio 1.19; 95% CI 1.04–1.36) compared with HT non-users.

When examined by type of hormone and compared with HT non-users, estrogen-only use was associated with an additional decline in mean eGFR over the study period (1.21 ml/min/1.73 m<sup>2</sup>; 95% CI 0.28–2.14), whereas there was no association between progestin-only or combination therapy and decline in eGFR (Table 2). In addition, risk of rapid loss of kidney function was increased by 17% for the estrogen-only users (odds ratio 1.17, 95% CI, 1.01–1.35) as compared with that for HT non-users. There was no increased risk of rapid loss of renal function associated with progestin-only or combination HT. Inclusion of angiotensin-converting enzyme inhibitor/angiotensin-receptor blocker or

non-steroidal anti-inflammatory drug use in the model did not change this relationship.

**Estrogen cumulative dose and chronic kidney disease progression**

Figure 2 outlines the distribution of cumulative estrogen dose for study subjects who were exposed to at least one form of estrogen (either alone or in conjunction with a progestin) and illustrates the linear relationship between cumulative estrogen dose and predicted change in mean eGFR. When cumulative dose was considered, there was a significant dose-response relationship between the cumulative dose of estrogen and the predicted change in mean eGFR. After adjusting for age, diabetes, comorbidity, and baseline eGFR, each increase of 100 defined daily dose of estrogen exposure (equivalent to 100 oral tablets of conjugated estrogen 0.625 mg) was associated with a decline in eGFR of 0.23 ml/min/1.73 m<sup>2</sup> (95% CI 0.10–0.37; P=0.001) over the study period.

**Route of administration and chronic kidney disease progression**

As compared with HT non-users, oral ingestion of estrogen (either alone or in conjunction with another route of administration) was associated with significant additional decline in eGFR over the study period, even after adjusting

for other covariates (1.86 ml/min/1.73 m<sup>2</sup> (95% CI 0.92–2.79; P=0.001), whereas use of transvaginal estrogen alone was not associated with loss of kidney function (Table 3). Inclusion of angiotensin-converting enzyme inhibitor, angiotensin-receptor blocker or non-steroidal anti-inflammatory drug use in the model did not change this relationship.

**DISCUSSION**

Our study is one of the first to examine the relationship between HT use and decline in kidney function in a large community-based elderly population. Compared with HT non-users, HT use was associated with a small, but statistically significant, decline in eGFR over the study period, even after adjustment for age, diabetes, baseline eGFR, and comorbidity. This effect was observed in estrogen-only users, and was present for oral but not transvaginal use. There also was evidence of a dose-response relationship between cumulative estrogen dose and loss of kidney function. Putting this into clinical context, compared with non-users of HT, eGFR was predicted to decrease by approximately 3 ml/min/1.73 m<sup>2</sup> more in a woman ingesting 0.625 mg of conjugated estrogen on a daily basis for 2 years, the average follow-up of our study.

Few studies have examined the effects of HT on change in kidney function. A small prospective study of 16 diabetic, hypertensive women ingesting a cyclic combination of oral

**Table 2 | Decline in eGFR over the study period for HT use compared with no use**

HT category	n	ΔeGFR (ml/min/1.73 m <sup>2</sup> ) (95% CI) <sup>a</sup>
None	4386	Reference
Estrogen only	1083	1.21 (0.28, 2.14)
Progestin only	40	3.98 (−0.30, 8.26)
Estrogen+progestin	336	0.99 (−0.56, 2.54)

CI, confidence interval; eGFR, estimated glomerular filtration rate; HT, hormone therapy.

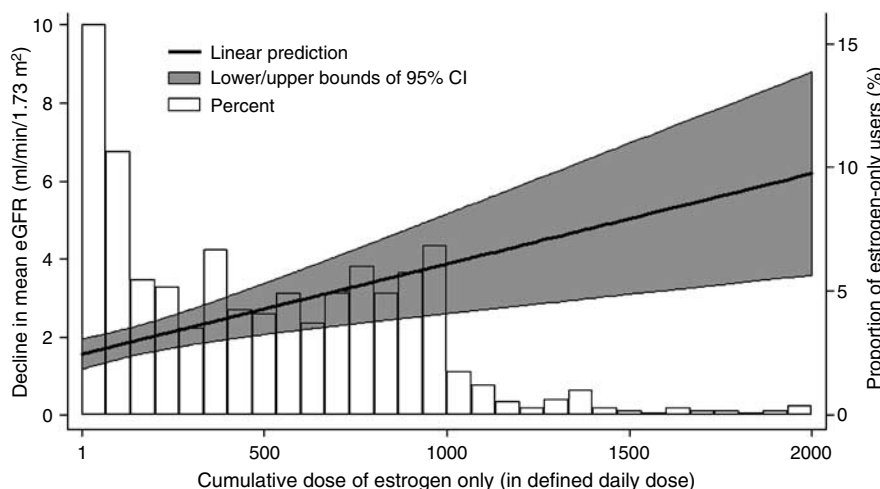
<sup>a</sup>Adjusted for baseline eGFR, age, diabetes, and comorbidity.

**Table 3 | Decline in eGFR over the study period for estrogen use compared with no HT use**

Route of administration	n	ΔeGFR (ml/min/1.73 m <sup>2</sup> ) (95% CI) <sup>a</sup>
None	4386	Reference
At least oral	1103	1.86 (0.92, 2.79)
Transvaginal only	331	−0.68 (−2.22, 0.86)
Other	25	0.71 (−4.69, 6.11)

CI, confidence interval; eGFR, estimated glomerular filtration rate; HT, hormone therapy.

<sup>a</sup>Adjusted for baseline eGFR, age, diabetes, and comorbidity.



**Figure 2 | Distribution of cumulative dose for subjects exposed to estrogen and relationship between estrogen exposure and predicted decline in mean eGFR. eGFR, estimated glomerular filtration rate.**

estradiol and norgestrel showed a small improvement in creatinine clearance after 3.5 monthly cycles,<sup>15</sup> and a large case-control study described better creatinine clearance for HT users compared with that for non-users.<sup>16</sup> In contrast, an observational study of 179 HT users and 312 non-users reported no change in eGFR over 5 years.<sup>17</sup> However, this study did not differentiate between users of estrogen, progestins, or combination therapy, which may explain some of the discrepancies in the study results. Additionally, the two larger studies did not control for route of HT administration; many of the effects of estrogen are mediated by first-pass effects on the liver, and thus result from oral, but not other, routes of administration of HT.<sup>18,19</sup>

Estrogen plays a role in the regulation of and response to some components of the renin-angiotensin system,<sup>20</sup> activation of which is well accepted to be deleterious to renal function.<sup>21</sup> Certainly, ingestion of exogenous estrogens contained in oral contraceptive results in increased activity of the renin-angiotensin system,<sup>22-25</sup> and increased risk of nephropathy has been reported in women with HT or oral contraceptive use.<sup>16,25,26</sup> In contrast, a high-estrogen state, such as pregnancy, is associated with decreased blood pressure despite increases in circulating components of the renin-angiotensin system,<sup>27</sup> suggesting that there are inherent differences between the actions of exogenous and endogenous estrogens. Estrogen therapy is also associated with increased activity of the vasodilator nitric oxide, although this effect may be tempered by the action of progesterone or synthetic progestins.<sup>28</sup>

We are unaware of any other study examining the effects of route of HT administration on renal function. Among routes of HT, oral ingestion predicted more rapid loss of kidney function compared with transvaginal use. It is well recognized that percutaneous administration of estrogens, in contrast to oral administration, circumvents first-pass gastrointestinal and liver metabolism, resulting in lower levels of estrogen metabolites, and does not cause induction of liver enzymes to the same degree as that associated with oral therapy.<sup>18</sup> Compared with oral formulations, transdermal estradiol appears to have more favorable effects on many intermediate cardiovascular disease risk markers.<sup>14</sup> Although clinical significance of the differences in pharmacokinetic and pharmacodynamic profiles between the oral and transdermal administration of HT is not fully known; particularly in chronic kidney disease,<sup>29,30</sup> transdermal delivery of estrogen may be a safer alternative in women with hypertension<sup>31</sup> or the metabolic syndrome.<sup>32</sup> Due to the 'uterine first-pass effect', hormones delivered transvaginally concentrate in the uterus and nearby tissues with low systemic exposure;<sup>19</sup> this may have also played a role in the lack of renal effects observed in our study with the transvaginal hormone preparations.

In our study, we were unable to control for timing of HT initiation (perimenopausal versus postmenopausal), or exposure to HT in the pre-study period, which may be important factors.<sup>33,34</sup> Most of the women in the Nurses'

Health Study, which suggested an estrogen-mediated protective effect on the cardiovascular system, started HT in the perimenopausal period. In contrast, the average age of subjects in the Women's Health Initiative trial,<sup>10</sup> which failed to demonstrate any cardioprotective effect with exogenous estrogen, was 10 years after menopause.<sup>35</sup> Continuous, but not intermittent, estradiol replacement prevented progression of glomerulosclerosis in ovariectomized rats,<sup>36</sup> suggesting that timing of initiation of HT plays a significant role in kidney function. Indeed, in the study demonstrating an improvement in albuminuria with HT use, most women began therapy in the perimenopausal period.<sup>17</sup> Nevertheless, one can interpret from our data that in the elderly postmenopausal state use of HT, or at least oral estrogen, appears to accelerate the decline of renal function.

This study has limitations. First, we were restricted in our assessment of clinical data. Although we could not confirm the postmenopausal state, the median age of menopause was found to be 51 years,<sup>37</sup> and our subjects were  $\geq 66$  years. We could not control for clinical factors such as blood pressure, proteinuria, smoking, obesity, or over-the-counter or herbal medication use, raising the possibility of residual confounding. However, in observational studies, women who take HT are generally better educated, have higher incomes and better access to health care, and are healthier even before starting therapy;<sup>33,38</sup> thus, it is possible that the risk demonstrated with HT use in our study may actually be an underestimate. While studies involving humans and animals have suggested that androgens can increase blood pressure and compromise renal function,<sup>39</sup> exclusion of the 24 subjects on combined estrogen and testosterone did not change the results. While there are diverse metabolic and clinical effects of different types of both estrogens and progestins,<sup>26,40</sup> our study was not powered to analyze the renal consequences by use of the individual synthetic hormone preparations. While there is potential for misclassification by categorization of data with respect to 'rapid loss of kidney function', our secondary outcome, this would not affect the primary outcome of our study (change in eGFR). Finally, we did not calibrate serum creatinine measurements with the Cleveland Clinic laboratory from which the Modification of Diet in Renal Disease (MDRD) equation is derived; however, given our primary interest was the change of kidney function, rather than the absolute value, this should not have influenced our findings.

Our study has many strengths. It is the first to examine the impact of cumulative estrogen dose and route of administration on renal function. The size of the cohort and its community-based setting increase the generalizability of our findings, and the pattern of HT use reported is similar to that in other studies.<sup>41</sup> Previous studies have demonstrated that the duration of our follow-up is adequate to determine loss of kidney function,<sup>42</sup> and the use of computerized drug prescription data eliminates the impact of recall bias.

In this elderly community-based population, HT in the form of oral estrogen use was associated, in a dose-dependent manner, with increased risk of loss of kidney function,

suggesting that surveillance of renal function may be prudent in the postmenopausal woman on HT. Although it remains unclear as to whether or not the effects of HT use on the kidney persist after discontinuation of medication, or whether timing of initiation or duration of use plays a role, the association between estrogen use, and oral estrogen in particular, and loss of kidney function in our study merits attention, although confirmatory studies should be performed prior to proposing changes to clinical practice.

## MATERIALS AND METHODS

### Study population

The Conjoint Ethics Review Board at the University of Calgary approved this study. A cohort of elderly female subjects aged  $\geq 66$  years was identified from the Calgary Laboratory Services database in Calgary, Alberta, Canada. This laboratory provides testing for the entire Calgary Health Region (catchment population 1.1 million) using a single regional laboratory and standardized methods that are recalibrated routinely against reference samples. To be eligible for inclusion, participants required at least one serum creatinine measurement in each of two study periods: 1 July 2001 to 31 December 2001; 1 and July 2003 to 31 December 2003. To reduce the impact of episodes of acute renal failure, laboratory measurements associated with a hospital admission were not included. Subjects were also excluded from the cohort if they had more than 12 outpatient serum creatinine measurements in either of the 6-month observation periods, as they were likely to represent patients with acutely unstable kidney function.<sup>5</sup> Renal transplant recipients or subjects receiving dialysis prior to study entry were also excluded.

### Measurement of kidney function and definition of outcomes

eGFR was used to estimate kidney function using the abbreviated MDRD equation, which includes variables for age, sex, race, and serum creatinine,<sup>43</sup> and has been validated for use for the elderly.<sup>44</sup> Although data for race were not available for the cohort, less than 1% of the Alberta population is Black; therefore, the impact at the population level of eliminating race from the estimate of GFR was expected to be minimal. Furthermore, given the study's focus on change in eGFR, information on race was not necessary. Because of concerns about the validity of the MDRD equation for subjects with higher levels of kidney function,<sup>45</sup> subjects with baseline eGFR values exceeding 90 ml/min/1.73 m<sup>2</sup> were excluded.

Serum creatinine measurements were analyzed in the same laboratory, thus eliminating the potential for inter-laboratory measurement variation. However, because of possible intra-laboratory variation in measurement resulting from changes in calibration of serum creatinine assays, measurements between the two time periods were assessed and calibrated in the following manner. First, a subset of healthy subjects (defined as subjects with no prescriptions for medications commonly used to treat cardiovascular disease, hypertension, or diabetes mellitus in the year before the index GFR) younger than 80 years of age was identified. Median serum creatinine measurement for these subjects, by 1-year age increments, for the 2001 and the 2003 time periods was then calculated. The difference between measurements for the two periods was calculated, and the average of the differences determined. To correct for systematic differences in serum creatinine measurements evident from this analysis, 2  $\mu\text{mol/l}$  (0.02 mg/dl) was subtracted from the serum creatinine measurements in 2003.

The primary outcome was the change in the mean eGFR in ml/min/1.73 m<sup>2</sup> between 2001 and 2003 (mean eGFR 2003 – mean eGFR 2001) for each subject. The secondary outcome was rapid loss of kidney function, defined as a decrease in eGFR  $\geq 4$  ml/min/1.73 m<sup>2</sup>/year, which is more than a twofold increase in the rate of decline expected for this population.<sup>5</sup>

### Measure of exposure

Using the unique provincial health care number for each subject, laboratory data were linked to the provincial administrative Alberta Blue Cross database to obtain information on prescription drug use for the exposure period 1 July 2000 to 31 March, 2003 (representing the end of the fiscal year for which drug data was available). All residents of Alberta aged  $\geq 66$  years receive insured health services, including coverage for prescription drugs. HT exposure (for the period of 1 year prior to initial eGFR measurement up to 31 March 2003) was defined using two approaches.

The first approach measured the presence or absence of exposure to HT, using four mutually exclusive categories: (1) non-users: no use of any HT; (2) estrogen and progestin users combined: at least one prescription for estrogen and at least one prescription for progestin; (3) estrogen user only: at least one prescription for estrogen with no prescriptions for progestin; and (4) progestin user only: at least one prescription for progestin with no prescriptions for estrogen.

The second approach measured the cumulative HT dose received during the exposure period, using the anatomical chemical therapeutic code and defined daily dose (DDD), to standardize estrogen and progestin exposure as follows:

$$\text{drug exposure} = \text{drug strength} \times \text{drug quantity} / \text{DDD}^{46}$$

The final approach categorized hormone exposure by 'route of administration': (1) none (reference); (2) at least oral; (3) transvaginal only; and (4) other. Transvaginal hormone preparations were considered a separate category, as this route of administration not only bypasses the first-pass effect (as opposed to oral formulations), but also results in low systemic availability of hormones.<sup>19</sup> 'Other' category of use included users of transdermal ( $n = 5$ ) or injectable HT preparations.

### Measure of covariates

Subjects were identified as having diabetes if they received at least one prescription for insulin or an oral hypoglycemic agent in the year before their index serum creatinine measurement. A measurement of comorbidity status, based on the use of prescription drugs, was calculated using the Chronic Disease Score.<sup>47</sup> The Chronic Disease Score is a validated weighted index of prescription medications; the greater the number of classes of medications dispensed, or the seriousness of the disease treated, the higher the score.

### Statistical methods

Baseline characteristics by type of HT user are presented as the mean  $\pm$  s.d. for normally distributed continuous variables and proportions for dichotomous variables. Differences in baseline characteristics across categories of HT use were determined by  $\chi^2$ -test, analysis of variance, and Kruskal–Wallis analysis, where appropriate. The association between HT use (non-users (reference), estrogen only, progestin only, and estrogen plus progestin) and loss of kidney function was assessed using multivariate linear regression, adjusting for age, baseline eGFR, diabetes, and comorbidity score.

A similar analysis was performed to determine the association between the route of HT administration (none, at least oral, transvaginal only, and other), as well as cumulative HT dose (DDD) and loss of kidney function. Finally, logistic regression was used to determine the association between HT use categories and rapid loss of kidney function, adjusting for covariates as previously described. In all analyses, non-HT users formed the reference group. Assumptions for both linear and logistic regression models were tested and met. All analyses were conducted using SAS (version 9.13; SAS Institute Inc., Cary, NC, USA) or Stata (version 9.1; Stata Corp., College Station, TX, USA) with two-tailed significance levels of 0.05.

## DISCLOSURE

All the authors declared no competing interests.

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