

# Serum vitamin D levels among patients in a clinical oncology practice compared to primary care patients in the same community: a case–control study

Thomas M Churilla,<sup>1</sup> Samuel L Lesko,<sup>1,2</sup> Harmar D Brereton,<sup>1,3</sup> Mary Klem,<sup>3</sup> Patrick E Donnelly,<sup>4</sup> Christopher A Peters<sup>1,3</sup>

**To cite:** Churilla TM, Lesko SL, Brereton HD, *et al.* Serum vitamin D levels among patients in a clinical oncology practice compared to primary care patients in the same community: a case–control study. *BMJ Open* 2011;**1**: e000397. doi:10.1136/bmjopen-2011-000397

► Prepublication history for this paper is available online. To view these files please visit the journal online (<http://bmjopen.bmj.com>).

Received 18 September 2011  
Accepted 21 November 2011

This final article is available for use under the terms of the Creative Commons Attribution Non-Commercial 2.0 Licence; see <http://bmjopen.bmj.com>

<sup>1</sup>The Commonwealth Medical College, Scranton, Pennsylvania, USA

<sup>2</sup>Northeast Regional Cancer Institute, Scranton, Pennsylvania, USA

<sup>3</sup>Northeast Radiation Oncology Center, Dunmore, Pennsylvania, USA

<sup>4</sup>Princeton University, Department of Chemistry, Frick Laboratory, Princeton, New Jersey, USA

**Correspondence to**  
Thomas M Churilla;  
[churillat2@gmail.com](mailto:churillat2@gmail.com)

## ABSTRACT

**Objectives:** Low serum vitamin D levels have been associated with risk for certain malignancies, but studies have not directly analysed levels between community oncology and primary care practices. The purpose of this study was to compare serum vitamin D levels in patients at a community oncology practice with non-cancer patients at a primary care practice.

**Design:** Retrospective case–control study. 25-Hydroxyvitamin D levels were ordered for screening in both cancer and non-cancer patients. Levels were compared in univariate and multivariate analyses adjusted for age, body mass index and season of blood draw.

**Setting:** A community-based radiation oncology centre and a community-based primary care practice: both located in Northeastern Pennsylvania, USA.

**Participants:** 170 newly diagnosed cancer patients referred for initial consultation at the community oncology centre from 21 November 2008 to 18 May 2010, and 170 non-cancer patients of the primary care practice who underwent screening for hypovitaminosis D for the first time from 1 January 2009 to 31 December 2009.

**Primary and secondary outcome measures:** The primary outcome measure was mean serum vitamin D level, and the secondary outcome measures were frequencies of patients with vitamin D levels <20 ng/ml and levels <30 ng/ml.

**Results:** The oncology patients had a significantly lower mean serum vitamin D level (24.9 ng/ml) relative to a cohort of non-cancer primary care patients (30.6 ng/ml,  $p<0.001$ ) from the same geographical region. The relationship retained significance after adjustment for age, body mass index and season of blood draw in multivariate analysis ( $p=0.001$ ). Levels <20 and <30 ng/ml were more frequent in the oncology patients (OR (95% CI)=2.59 (1.44 to 4.67) and 2.04 (1.20 to 3.46), respectively) in multivariate analysis.

**Conclusions:** Cancer patients were found to have low vitamin D levels relative to a similar cohort of non-cancer primary care patients from the same geographical region.

## ARTICLE SUMMARY

### Article focus

- Our study sought to analyse vitamin D levels in large outpatient oncology and primary care centres.

### Key messages

- Multiple levels of evidence suggest an association between low vitamin D and cancer.
- Our findings of low vitamin D among the oncology patients add practical relevance to this association since we analysed patients at community clinics.
- Providers caring for cancer patients should be aware of an increased incidence of hypovitaminosis D at the community level.

### Strengths and limitations

- Limitations include a relatively small sample size, lack of data on comorbid conditions of the primary care group, lack of data on vitamin D measurement and lack of data on supplementation or treatment that may have affected vitamin D levels.
- Strengths include a community-based sample in both primary care and oncology patients and control of age, body mass index, latitude, time and season of blood draw and geographical region of both patient groups.

## INTRODUCTION

Vitamin D, obtained through the diet, supplementation and sunlight, is converted to 25-hydroxyvitamin D in the liver.<sup>1</sup> 25-Hydroxyvitamin D is the major circulating form of vitamin D and undergoes hydroxylation in the kidney to 1,25-dihydroxyvitamin D, the most active metabolite.<sup>1</sup> Production of 1,25-dihydroxyvitamin D is tightly regulated by the parathyroid glands in response to calcium.<sup>1</sup> Levels of 25-hydroxyvitamin D are

relatively stable and can be measured to determine the vitamin D status of a patient.<sup>1</sup> However, the definition of normal circulating vitamin D levels is debatable.<sup>1–2</sup> Values <20 ng/ml have been traditionally considered deficient (in accordance with the latest Institute of Medicine guidelines), whereas values <30 ng/ml have been suggested to be suboptimal.<sup>1–7</sup>

Non-skeletal actions of vitamin D have gained interest in research, particularly in the field of oncology. Low serum vitamin D levels have been associated with risk for carcinomas of the breast, prostate and colon in epidemiological studies.<sup>1–8–11</sup> Research dating back to the 1980s has proposed that variations in cancer by latitude may be associated with vitamin D through differences in ultraviolet B exposure.<sup>12–14</sup> Subsequent laboratory experiments have found that many cell types, in addition to renal and intestinal cells, possess vitamin D receptors and 25-hydroxyvitamin D 1-alpha-hydroxylase, the cellular machinery required to metabolise vitamin D.<sup>1–9–15–19</sup> In vitro studies have further demonstrated that vitamin D regulates genes involved with cellular proliferation and differentiation.<sup>1–9–16–20</sup> Taken together, this body of evidence suggests a potential role for vitamin D in the aetiology of cancer.

To date, studies have not directly compared vitamin D levels in community oncology and primary care practices in the same region. Analysing vitamin D levels in this manner may elucidate trends not previously apparent. Therefore, the purpose of this study was to compare vitamin D levels in patients at a community oncology practice with non-cancer patients at a primary care practice.

## MATERIALS AND METHODS

The study was a retrospective case–control design, and local institutional review board approval was obtained. The cases (cancer patients) consisted of a consecutive series of patients seen for initial radiation oncology consultation from 21 November 2008 to 18 May 2010 at a community-based oncology centre in Northeastern Pennsylvania, USA. Serum 25-hydroxyvitamin D levels were ordered at the initial visit. Data for the cases were collected through a manual review of medical records. The controls (primary care patients) were a random sample of patients with no history of cancer who were screened for the first time for hypovitaminosis D from 1 January 2009 to 31 December 2009 at a community-based primary care practice in Northeastern Pennsylvania, USA. Data for the controls were obtained by retrieval from an electronic health record. 25-hydroxyvitamin D levels were measured at outpatient laboratory centres, and three major companies were retrospectively identified: two using a chemiluminescent assay and one using an enzyme immunoassay.

MYSTAT 12 (Systat Software Inc., Chicago, Illinois, USA) and StatPlus 2009 Professional 5.8.4 (AnalystSoft Inc., Alexandria, Virginia, USA) were used for statistical analyses with significance defined as  $\alpha < 0.05$ . Origin 8.5

(OriginLab Corp., Northampton, Massachusetts, USA) was used to generate histograms and best-fit Gaussian distributions. Student *t* test was performed to compare vitamin D levels between oncology and non-cancer patients. Multiple linear regression was used to adjust the mean difference for age, body mass index (BMI) and season of blood draw. In multiple linear regression, vitamin D levels were set as the dependent variable (continuous), and the independent variables were set as case–control status (dichotomous), age (continuous), BMI (continuous) and season of blood draw (dichotomous). The coefficient for case–control status represented the mean difference in serum vitamin D levels between the oncology and primary care patients, after adjustment for age, BMI and season of blood draw.

The prevalence of vitamin D deficiency (<20 ng/ml) and vitamin D insufficiency (<30 ng/ml) were examined with respect to case–control status by calculating the OR and computing Pearson's  $\chi^2$  test. Multiple logistic regression was used to adjust associations for age, BMI and season of blood draw. In multiple logistic regression analyses, frequencies of patients with vitamin D levels less than the cut-off value (20 or 30 ng/ml) were set as the dependent variable (dichotomous) and the independent variables were set as case–control status (dichotomous), age (continuous), BMI (continuous) and season of blood draw (dichotomous). In all multivariate analyses, season of blood draw was adjusted as a dichotomous variable defined as summer months (June, July or August) versus all other months. Patients with missing data were excluded from the multivariate analyses.

## RESULTS

One hundred and seventy cancer patients had levels drawn within 6 months of consultation at the community radiation oncology centre. The most common primary cancer sites were as follows: breast (40), prostate (35), thyroid (25) and lung (12). The distribution of the American Joint Committee on Cancer (AJCC) stages of cancer was as follows: stage 0 (6), stage I (47), stage II (52), stage III (32), stage IV (25) and unknown stage (8). One hundred and seventy non-cancer patients screened for hypovitaminosis D for the first time had vitamin D levels drawn at a large, community-based primary care practice. The baseline patient characteristics are outlined in table 1. The cancer patients were an average of 6.8 years older ( $p < 0.001$ ), but both groups had a similar mean BMI ( $p = 0.637$ ). The frequency distribution of vitamin D levels in the primary care and oncology groups is shown in figure 1.

The cancer patients had a significantly lower mean serum vitamin D level, and this relationship retained significance after adjustment for age, BMI and season of blood draw. Table 1 outlines the unadjusted mean values and adjusted mean difference of serum vitamin D levels between cancer and non-cancer patients. The primary care patients had a mean serum vitamin D level of 30.6 ng/ml, while the cancer patients had a mean serum

**Table 1** Baseline patient characteristics and serum vitamin D levels in oncology patients and non-cancer primary care patients

	Oncology	Primary care	p Value	OR (95% CI)*
Sample size (n)	170	170	—	—
Age ( $\pm$ SD), years	63.3 ( $\pm$ 14.8)	56.5 ( $\pm$ 16.3)	<0.001	—
BMI ( $\pm$ SD), kg/m <sup>2</sup>	29.3 ( $\pm$ 7.1) <sup>†</sup>	28.9 ( $\pm$ 5.8)	0.637	—
Blood drawn in summer months, count (%)	44 (25.9)	31 (18.2)	0.089	—
Vitamin D levels				
Mean (SD), ng/ml	24.9 (11.4)	30.6 (12.5)	<0.001 <sup>‡</sup>	—
Adjusted mean difference, ng/ml	5.4		0.001 <sup>§</sup>	—
Patients <30 ng/ml, count (%)	126 (74)	94 (55)	0.008*	2.04 (1.20 to 3.46)
Patients <20 ng/ml, count (%)	56 (33)	29 (17)	0.002*	2.59 (1.44 to 4.67)

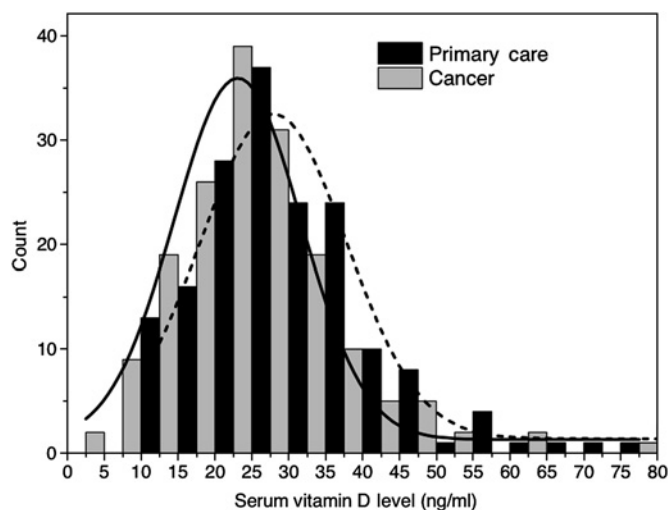
BMI, body mass index.

\*Multiple logistic regression adjusted for age, BMI and season of blood draw.

<sup>†</sup>BMI for cancer patients was based on data of 110 patients.<sup>‡</sup>Student t test.<sup>§</sup>Multiple linear regression adjusted for age, BMI and season of blood draw.

vitamin D level of 24.9 ng/ml ( $p < 0.001$ ). After adjustment for age, BMI and season of blood draw, the mean difference in serum vitamin D levels was 5.4 ng/ml ( $p = 0.001$ ).

Vitamin D deficiency, defined as <20 ng/ml, was more common in the oncology practice (OR (95% CI)=2.39 (1.43 to 3.99),  $p = 0.001$ ); vitamin D insufficiency, defined as <30 ng/ml, was also more common in the oncology practice (OR (95% CI)= 2.32 (1.47 to 3.66),  $p < 0.001$ ). The relationships retained significance in multivariate analysis after correction for age, BMI and season of blood draw, as shown in [table 1](#). Vitamin D deficiency and vitamin D insufficiency were more common in the oncology patients in multivariate analysis (OR (95% CI)=2.59 (1.44 to 4.67) and 2.04 (1.20 to 3.46), respectively).



**Figure 1** Frequency distribution of 25-hydroxyvitamin D levels in primary care patients (dark grey bars) and oncology patients (light grey bars). The mean (SD) vitamin D levels were 24.9 (11.4) ng/ml for oncology patients and 30.6 (12.5) ng/ml for primary care patients. The best-fit Gaussian distributions are represented as a solid curve for oncology patients and a dashed curve for the primary care patients.

## DISCUSSION

While the definition of an acceptable range of serum vitamin D levels is debatable,<sup>1 2</sup> patients seen at the oncology clinic displayed significantly reduced serum levels of 25-hydroxyvitamin D relative to a geographically similar group of non-cancer patients ([table 1](#) and [figure 1](#)). While the primary care patients had a mean around 30 ng/ml, a value deemed sufficient by many experts,<sup>1</sup> 55% of patients fall below this value as indicated by the positive skew in the histogram. The vitamin D levels in oncology patients also display positive skew, with a visibly lower mean of approximately 25 ng/ml. The combined best-fit Gaussian distribution curves illustrate a lower distribution of vitamin D levels in the oncology patients relative to the primary care patients.

The reduced serum vitamin D levels seen in the cancer patients may be either a cause or effect relationship. Multiple studies have found increased cancer risk in individuals with decreased serum vitamin D levels and may explain the association in our data.<sup>1 8–11</sup> However, it is also possible that a diagnosis of cancer promotes reduced vitamin D levels due to poor oral intake or decreased sun exposure. Regardless of the mechanism, these data suggest that increased clinical suspicion of vitamin D deficiency in cancer patients may be reasonable among the primary care community.

There are several limitations that should be considered while interpreting the data. First, the laboratory used to determine 25-hydroxyvitamin D levels in both the cancer patients and the non-cancer patients was not controlled. Patients received orders for 25-hydroxyvitamin D and had levels drawn at outpatient laboratories, most of which used either a chemiluminescent assay or enzyme immunoassay for 25-hydroxyvitamin D determination. These two methods are thought to be comparable in accuracy and precision.<sup>21</sup> Since patients at either clinic resided in the same geographical location, it is unlikely that there were important differences in measurement of vitamin D between or within the groups. Second, conditions that may affect vitamin D

levels, such as treatment in cancer patients or comorbid conditions in primary care patients, were not accounted for in the analysis. Third, BMI data were available for only 110 of the 170 oncology patients. Since patients with missing data were excluded from multivariate analyses, the sample size was reduced among the oncology patients. Finally, gender, supplement use and race were not controlled for in the analysis, although the vast majority of the patient pool was Caucasian.

Considering the limitations, there are several strengths to the analysis. The oncology and primary care practices serve the same geographical area; therefore, latitude and regional trends were similar between the groups. In addition, the cancer and non-cancer patients had levels drawn during a similar time frame in 2009 (only 12 cancer patients had levels drawn outside of 2009). Thus, the reduced levels seen in the oncology patients relative to the non-cancer patients were independent of age, BMI, latitude, time and season of blood draw and geographical region. Finally, our data may have practical relevance to physicians in private practice since both of our patient populations were derived from community-based practices.

## CONCLUSIONS

Low levels of 25-hydroxyvitamin D were observed in both the community oncology practice and the primary care practice. However, the cancer patients had significantly lower levels of circulating vitamin D. A heightened awareness for vitamin D deficiency among cancer patients may be appropriate based on the results of this study.

**Acknowledgements** The authors thank Ms Melanie Walker for assistance in data collection. TMC would like to thank the Commonwealth Medical College for partial financial support for the study.

**Funding** TMC received a medical student research stipend through the Commonwealth Medical College for partial financial support during the study. This research received no specific grant from any funding agency in the public, commercial or not for profit sectors.

**Competing interests** None.

**Ethics approval** This study was approved by the Scranton Temple Residency Program Institutional Review Board.

**Contributors** TMC participated in data collection through chart review, intellectual analysis of data and writing of paper. SLL participated in data acquirement, intellectual analysis of data and editing of paper. HDB participated in intellectual planning of project, recruitment of patients and

editing of paper. MK participated in intellectual planning of project, data collection and editing of paper. PED participated in intellectual analysis of data, production of figure and editing of paper. CAP participated in intellectual planning of project, recruitment of patients, intellectual analysis of data and editing of paper.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data sharing statement** No additional data available.

## REFERENCES

- Holick M. Vitamin D deficiency. *N Engl J Med* 2007;357:266–81.
- Thacher TD, Clarke BL. Vitamin D insufficiency. *Mayo Clin Proc* 2011;86:50–60.
- Holick MF, Siris ES, Binkley N, *et al*. Prevalence of Vitamin D inadequacy among postmenopausal North American women receiving osteoporosis therapy. *J Clin Endocrinol Metab* 2005;90:3215–24.
- Heaney RP, Dowell MS, Hale CA, *et al*. Calcium absorption varies within the reference range for serum 25-hydroxyvitamin D. *J Am Coll Nutr* 2003;22:142–6.
- Dawson-Hughes B, Heaney RP, Holick MF, *et al*. Estimates of optimal vitamin D status. *Osteoporos Int* 2005;16:713–16.
- Slomski A. IOM endorses vitamin D, calcium only for bone health, dispels deficiency claims. *JAMA* 2011;305:453–4, 6.
- Institute of Medicine. *Dietary Reference Intakes for Calcium and Vitamin D*. Washington, DC: Institute of Medicine, 2011.
- Giovannucci E. The epidemiology of vitamin D and cancer incidence and mortality: a review (United States). *Cancer Causes Control* 2005;16:83–95.
- Schwartz G, Skinner H. Vitamin D status and cancer: new insights. *Curr Opin Clin Nutr Metab Care* 2007;10:6–11.
- Ahonen MH, Tenkanen L, Teppo L, *et al*. Prostate cancer risk and prediagnostic serum 25-hydroxyvitamin D levels (Finland). *Cancer Causes Control* 2000;11:847–52.
- Feskanich D, Ma J, Fuchs C, *et al*. Plasma vitamin D metabolites and risk of colorectal cancer in women. *Cancer Epidemiol Biomarkers Prev* 2004;13:1502–8.
- Garland C, Garland F. Do sunlight and vitamin D reduce the likelihood of colon cancer? *Int J Epidemiol* 2006;35:217–20.
- Luscombe CJ, Fryer AA, French ME, *et al*. Exposure to ultraviolet radiation: association with susceptibility and age at presentation with prostate cancer. *Lancet* 2001;358:641–2.
- Hanchette CL, Schwartz GG. Geographic patterns of prostate cancer mortality. Evidence for a protective effect of ultraviolet radiation. *Cancer* 1992;70:2861–9.
- Giovannucci E. Vitamin D status and cancer incidence and mortality. *Adv Exp Med Biol* 2008;624:31–42.
- Polek T, Weigel N. Vitamin D and prostate cancer. *J Androl* 2002;23:9–17.
- Davis C. Vitamin D and cancer: current dilemmas and future research needs. *Am J Clin Nutr* 2008;88:565S–9S.
- Bikle D. Nonclassic actions of vitamin D. *J Clin Endocrinol Metab* 2009;94:26–34.
- Samuel S, Sitrin M. Vitamin D's role in cell proliferation and differentiation. *Nutr Rev* 2008;66(10 Suppl 2):S116–24.
- Nagpal S, Na S, Rathnachalam R. Noncalcemic actions of vitamin D receptor ligands. *Endocr Rev* 2005;26:662–87.
- Wallace AM, Gibson S, de la Hunty A, *et al*. Measurement of 25-hydroxyvitamin D in the clinical laboratory: current procedures, performance characteristics and limitations. *Steroids* 2010;75:477–88.



STROBE Statement—Checklist of items that should be included in reports of *case-control studies*

	Item No	Recommendation
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract <b>(Page 2)</b> (b) Provide in the abstract an informative and balanced summary of what was done and what was found <b>(Page 2-3)</b>
<b>Introduction</b>		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported <b>(Page 5-6)</b>
Objectives	3	State specific objectives, including any prespecified hypotheses <b>(Page 6)</b>
<b>Methods</b>		
Study design	4	Present key elements of study design early in the paper <b>(Page 6)</b>
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection <b>(Page 6)</b>
Participants	6	(a) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <b>(Page 6)</b> (b) For matched studies, give matching criteria and the number of controls per case <b>(N/A)</b>
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable <b>(Page 7)</b>
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group <b>(Page 7)</b>
Bias	9	Describe any efforts to address potential sources of bias <b>(Page 7)</b>
Study size	10	Explain how the study size was arrived at <b>(Page 6-7)</b>
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why <b>(Page 7)</b>
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding <b>(Page 7)</b> (b) Describe any methods used to examine subgroups and interactions <b>(N/A)</b> (c) Explain how missing data were addressed <b>(Page 8)</b> (d) If applicable, explain how matching of cases and controls was addressed <b>(N/A)</b> (e) Describe any sensitivity analyses <b>(N/A)</b>
<b>Results</b>		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed <b>(Page 8)</b> (b) Give reasons for non-participation at each stage <b>(N/A)</b> (c) Consider use of a flow diagram <b>(N/A)</b>
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders <b>(Page 8, Table 1)</b> (b) Indicate number of participants with missing data for each variable of interest <b>(Table 1: legend point 2)</b>
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure <b>(N/A)</b>
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were

		adjusted for and why they were included ( <b>Page 8-9</b> )
		(b) Report category boundaries when continuous variables were categorized ( <b>Page 7</b> )
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period ( <b>N/A</b> )
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses ( <b>Response to Decision Letter Page 3-4</b> )
<b>Discussion</b>		
Key results	18	Summarise key results with reference to study objectives ( <b>Page 11-12</b> )
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias ( <b>Page 11</b> )
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence ( <b>Page 11-12</b> )
Generalisability	21	Discuss the generalisability (external validity) of the study results ( <b>Page 11-12</b> )
<b>Other information</b>		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based ( <b>Page 16</b> )

\*Give information separately for cases and controls.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.