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Smoking in Dialysis Patients: A Systematic Review and Meta-analysis of Mortality and Cardiovascular Morbidity

Scott E. Liebman, MD[*],
University of Rochester Medical Center

Steven P. Lamontagne, MD,
University of Rochester Medical Center

Li-Shan Huang, PhD,
Institute of Statistics, National Tsing Hua University, Hsin-Chu city, TAIWAN R.O.C

Susan Messing, MS, and
Department of Biostatistics and Computational Biology, University of Rochester Medical Center

David A. Bushinsky, MD
University of Rochester Medical Center

Abstract

Background—Cigarette smoking is associated with increased cardiovascular morbidity and mortality in the general population, but the effect of smoking on these outcomes in the dialysis population is less well studied.

Study Design—Systematic review and meta-analysis of cohort studies.

Setting & Population—Adults treated with long-term hemodialysis or peritoneal dialysis.

Selection Criteria for Included Studies—Cohort studies of unselected dialysis patients reporting the association between smoking status and cardiovascular morbidity and/or mortality.

Predictor—Smoking status (determined by patient report).

Outcomes—1) All-cause or cardiovascular mortality; 2) Incident cardiovascular events

Results—We identified 34 studies which fulfilled all inclusion criteria. Of these, 26 studies provide data on smoking and mortality and 10 (n = 6538) were included in a meta-analysis. The pooled hazard ratio for all-cause mortality in smokers compared to non-smokers was 1.65 (95% CI , 1.26–2.14; p<0.001) Eleven studies provided data on smoking and incident cardiovascular events, 5 (pooled n = 845) were included in a meta-analysis. The pooled hazard ratio for composite cardiovascular events in smokers compared to non-smokers was 1.01 (95% CI, 0.98–1.05, p 0.4)..

Limitations—Data for these meta-analyses were heterogeneous. Few individual studies assessed smoking as the primary variable of interest.

[*]601 Elmwood Avenue, Box 675, Rochester, NY 14642, (585) 275-4517, Fax (585) 442 – 9201, Scott_Liebman@urmc.rochester.edu.

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Conclusions—Active smoking is associated with a significant increase in all-cause mortality in dialysis patients, although there was not a corresponding increased risk of cardiovascular events.

In the general population the adverse health effects of cigarette smoking are well known. Smoking is the leading cause of preventable mortality in the US and accounts for approximately 443,000 deaths annually with 28% due to ischemic heart disease. [1] Internationally, smoking accounts for 1.6 million cardiovascular deaths each year with 54% due to ischemic heart disease and 25% due to cerebrovascular disease. [2] Despite the negative consequences of smoking, tobacco use remains common in the United States. The Center for Disease Control estimates that in 2008, approximately one out of five American adults were active smokers [3]. The prevalence of smoking in dialysis patients is less clear. The most recent USRDS estimate, based on data from the End Stage Renal Disease Medical Evidence Report (Form 2728) as completed by dialysis providers, is that 6.2% of incident dialysis patients are smokers [4]. However, the provider-generated data in the 2728 form has been shown to significantly underestimate true smoking prevalence [5]. Dialysis patient questionnaires estimate the true prevalence of cigarette smoking to be between 14 and 15%.[5]

Amongst disease-specific populations, it would seem that individuals with end-stage renal disease (ESRD) would be especially vulnerable to the adverse consequences of smoking. The annual mortality in the dialysis population is very high with only 34% five-year survival [4, 6]. Cardiovascular disease accounts for 40 % of all deaths in this population [4, 6].

Given that patients with ESRD have a high rate of cardiovascular disease, as do smokers with normal kidney function, we hypothesized that ESRD patients who smoke would be at extraordinarily high risk of cardiovascular disease and subsequent mortality. The answer to this question may seem obvious; however, several co-morbidities associated with increased mortality in the general population such as hypercholesterolemia [7, 8] hypertension [9] and obesity [10, 11] have not been shown to increase mortality in the ESRD population [12–14]. In this study we systematically reviewed all publications that compared ESRD smokers to non-smokers with regards to mortality and/or cardiovascular morbidity.

Methods

Study Selection

A Medline search from 1970-present was conducted on January 17, 2011 with no language restrictions using the following criteria: “smoking AND (dialysis OR hemodialysis OR end stage renal disease OR chronic kidney disease OR chronic renal failure)” (Item S1, available as online supplementary material). Animal or pediatric studies (subjects under 19 years of age) were excluded without further review. Abstracts of the remaining studies were reviewed by two independent reviewers (S.E.L. and S.P.L), with any discrepancies adjudicated by an independent third party (D.A.B.). The reference lists for each of these studies and all of the references in the 2005 KDOQI guidelines on smoking in dialysis patients were also searched for relevant studies 15. In addition, all abstracts submitted to the American Society of Nephrology’s Renal Week annual meeting for the past three years were searched for potentially relevant data sets, and authors were contacted to provide data. Full text review of these studies was performed to assess fulfillment of the following inclusion criteria: cohort study design (either prospective or retrospective); unselected population comprised entirely of ESRD patients (treated either with hemodialysis or peritoneal dialysis); and compared between smokers and non-smokers one or more of the outcomes of interest. Outcomes of interest were either mortality (all-cause or cardiovascular) or cardiovascular morbidity (comprising incident cardiac events, incident peripheral vascular events, or incident cerebrovascular events).

Quantitative Data Synthesis

Given that only the estimates, not the individual data, from each study were available, we used a random effects meta-analysis model 16 to estimate the pooled hazard ratio with 95% confidence intervals (CIs). The random effects analysis calculates a weighted average of the estimates, and includes the original variance plus the between-studies variance. Thus the smaller the variances, the more weight an estimate will have in the pooled estimate. In all studies included, the adjusted hazard ratio was used for analysis. The presence of heterogeneity across studies was evaluated using Q-statistic. The analyses were carried out using "meta" package in software R version 2.12.1 on a WINDOWS XP platform.

Results

Study Identification

A summary of the study identification process is shown in Figure 1. The original Medline search indentified 1533 articles, this number decreased to 1047 with exclusion of animal or pediatric studies. Reference list review, ASN abstract search, and review of KDOQI citations identified an additional 10 articles. Of this total, 943 were excluded based on abstract review and 34 of the remaining studies fulfilled our inclusion criteria after full-text review. We divided studies by two outcomes - mortality or incident cardiovascular events. Several studies provided data on multiple outcomes of interest, and therefore there are a greater number of total outcomes analyzed than included studies. One article which fulfilled our inclusion criteria[17] was not included, as another study [18] analyzed the same dataset using smoking as the primary variable of interest, not simply as a covariate.

Risk of Bias

The majority of studies included in this review continued patient follow-up for several years time, a duration which should allow for a valid estimation of the true frequency of the outcomes assessed. Studies included in this review were comprised of representative samples of ESRD patients, although many cohorts were single-center and ethnically homogeneous. In addition, most included studies required that patients be stable on dialysis for 3 months and free of acute medical conditions (often active infection or heart failure) for enrollment, which likely excluded a high-risk population from analysis. Publication bias is unlikely in this review given that nearly all included studies reported data on the effect of smoking only as a covariate, and not as the main rationale for publication. For those studies included in meta-analysis, the relationship between smoking and the main outcome of interest was reported via a multivariate-adjusted Cox proportional hazard model, which allowed for the control of other factors (age, gender, and other co-morbidities) which could obscure this relationship.

Mortality

We identified 26 cohort studies examining the relationship between cigarette smoking and mortality in dialysis patients (Table 1). There are numerous differences between these studies including cohort size, dialysis modality, and the definition of smoking (i.e. both former and current cigarette users considered as "smokers" versus considering current smokers only, with some not explicitly defining smoking status). Most of these studies were single-center cohorts, had a small number of patients, and were not specifically designed to address the relationship between smoking and mortality. In most cases smoking status was analyzed only as a covariate.

Of the 26 total studies, two were specifically designed to investigate the relationship between smoking and mortality in ESRD patients and deserve additional attention. Foley et al. examined a large cohort (n=3941) of ESRD patients at the initiation of either peritoneal

dialysis (PD) or hemodialysis (HD) [18]. Patients were stratified into one of five groups based on their response to a questionnaire: lifelong non-smokers (56 %), current smokers (14 %), individuals who quit smoking more than 1 year prior (20 %), those who quit within one year (6 %), or status unknown (4 %). Compared to lifelong non-smoking, current smoking was associated with an increased risk of mortality (RR, 1.37) after adjustment for other demographic variables. Former smokers (even those who had quit within one year) were not at an increased mortality risk. Braatvedt et al. studied the relationship between smoking and mortality in a large cohort (n = 1293) of patients initiating PD [21]. Patients were categorized as smokers, including both current (17%) or former smokers (45%), or lifetime non-smokers (38%) based on an interview. After follow-up ranging from 20–140 months, mortality was significantly higher for smokers (current or former) compared to lifetime non-smokers (RR, 1.22). There was no significant difference in survival between former or current smokers.

Ten studies (pooled n = 6538) provided estimates of the hazard ratio for all-cause mortality in smokers versus non-smokers, and could be included in a meta-analysis. The pooled hazard ratio for mortality comparing smokers to non-smokers was 1.65 (95%CI, 1.26–2.14; $p<0.001$) based on a random effects analysis. (Figure 2). There was significant heterogeneity amongst studies, with a Q-statistic p value of 0.003.

Cardiovascular Morbidity

Eleven studies provided data on the relationship between cigarette smoking and a variety of cardiovascular events in the ESRD population (Table 2). The majority provided data for a composite cardiovascular outcome and were not specifically designed with smoking as the primary variable of interest. One study provided data for a variety of individual cardiovascular outcomes and was designed with smoking as the primary variable [18]. As described earlier, patients in this large cohort were classified as non-smokers, current smokers, or former smokers. Using inpatient Medicare claim records, the rate of incident cardiovascular outcomes was assessed prospectively in this group. Over a mean follow-up of 2.2 years, current smokers were more likely to develop heart failure (RR, 1.59) and peripheral vascular disease (RR, 1.68) compared to lifelong non-smokers. Current smoking did not have a statistically significant impact on the rates of incident ischemic heart disease or cerebrovascular disease, and former smoking conferred no excess risk compared to lifelong non-smoking on any cardiovascular outcome.

In the majority of the remaining studies, data were provided for a composite cardiovascular outcome – different in each study but generally a combination of ischemic heart events (myocardial infarction or need for percutaneous coronary intervention or coronary bypass surgery), cerebrovascular events (transient ischemic attack or stroke), or peripheral vascular events (arterial thrombosis or need for revascularization procedure or amputation). Some also included cardiovascular death, congestive heart failure, and deep venous thrombosis as part of the composite outcome.

Five studies (pooled n = 845) provided an estimate of the hazard ratio for composite cardiovascular outcomes in smokers versus non-smokers, and could be included in a meta-analysis. The pooled hazard ratio for incident cardiovascular events in smokers compared to non-smokers was 1.01 (95%CI, 0.98–1.05; p=0.4) based on a random effects analysis. (Figure 3).

Discussion

This review and meta-analysis summarizes the currently available data on the relationship between cigarette smoking and clinical outcomes in the ESRD population. With respect to mortality the data were heterogeneous, but the meta-analysis demonstrates a significantly

higher risk of mortality in dialysis patients who smoke compared to those who do not. In support of this finding, both studies specifically designed to evaluate the mortality risk of smoking showed significantly increased mortality in active smokers compared to non-smokers 18, 21. The estimated magnitude of this effect found on meta-analysis (a 49 % risk increase) is clinically significant, and should prompt the clinician to address smoking cessation in addition to the myriad of other factors known to impact mortality in the dialysis population.

The data were also heterogeneous for incident cardiovascular events, but showed no significant increased risk in smokers compared to non-smokers. Given the conclusive mortality increase in smokers, and the presumption that this is due to accelerated vascular disease, how can these data be reconciled? It may be that the composite cardiovascular outcome used in our meta-analysis included several manifestations of vascular disease which were not influenced by smoking status, with the overall result that a composite outcome showed a non-significant result. To support this, the two largest studies examining cardiovascular outcomes in an ESRD population 18, 45 demonstrated a higher incidence of peripheral vascular events and heart failure in smokers, but there was no increased incidence of cerebrovascular or coronary vascular events. Alternatively, smoking may increase mortality through non-cardiovascular mechanisms.

One strength of this review is that we focused our analysis on the most rigorous data available. Given that a randomized controlled trial of smoking in the ESRD population is not feasible, we focused on cohort studies in an attempt to isolate a direct temporal relationship between cigarette smoking and the outcomes of interest. We eliminated studies with unclear design as well as those which included only a specific ESRD subpopulation. Further, we limited our review to the clinical outcomes most pertinent to the care of ESRD patients, rather than focusing on biochemical markers or radiographic/angiographic evidence of vascular disease.

Limitations of this review are inherent in the design of the included studies. In all included studies, smoking status was defined at study outset only, and no data were provided regarding changes in smoking habits during follow up. Further, smoking status was determined by self report, which may lead to misclassification 51, 52. Finally, the majority of studies reported data on cigarette smoking only as a covariate along with another major variable of interest. As such, sample sizes may not have been adequate to detect outcome differences in relation to smoking status. This may have been a major factor in the overall heterogeneity of our meta-analyses.

There are many opportunities for further work in this area. Studies using objective biomarkers of nicotine exposure (such as cotinine [53]) may more accurately establish the relationship between cigarette smoking and adverse events. This would eliminate the potential misclassification bias introduced by self report. Also, the impact of successful smoking cessation on clinical outcomes in the ESRD population has not been evaluated. While significant, data from cohort studies can only demonstrate association, not causality. A demonstrated decrease in adverse events after smoking cessation would further compel providers to counsel against tobacco use. Studies examining the most successful means to achieve smoking cessation are also lacking in the ESRD population. Given the mortality benefit for non-smoking ESRD patients demonstrated in this review, a clinical trial to determine the most effective intervention (counseling versus the various forms of pharmacologic therapy) would be a logical next step.

The adverse effects of smoking in the ESRD population are less well-established than in the general population. Our meta-analysis shows that there is a significantly higher risk of

mortality in dialysis patients who smoke compared to those who do not. Based on current data, however, there does not appear to be a higher incidence of cardiovascular events in smokers versus non-smokers with ESRD. Given our findings, we support the 2005 KDOQI guidelines advocating regular counseling and encouragement to stop smoking in all ESRD patients [15].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Developmental Toxicology. Therapeutic Drug Monitoring. 2009; 31(1):14–30. [PubMed: 19125149]

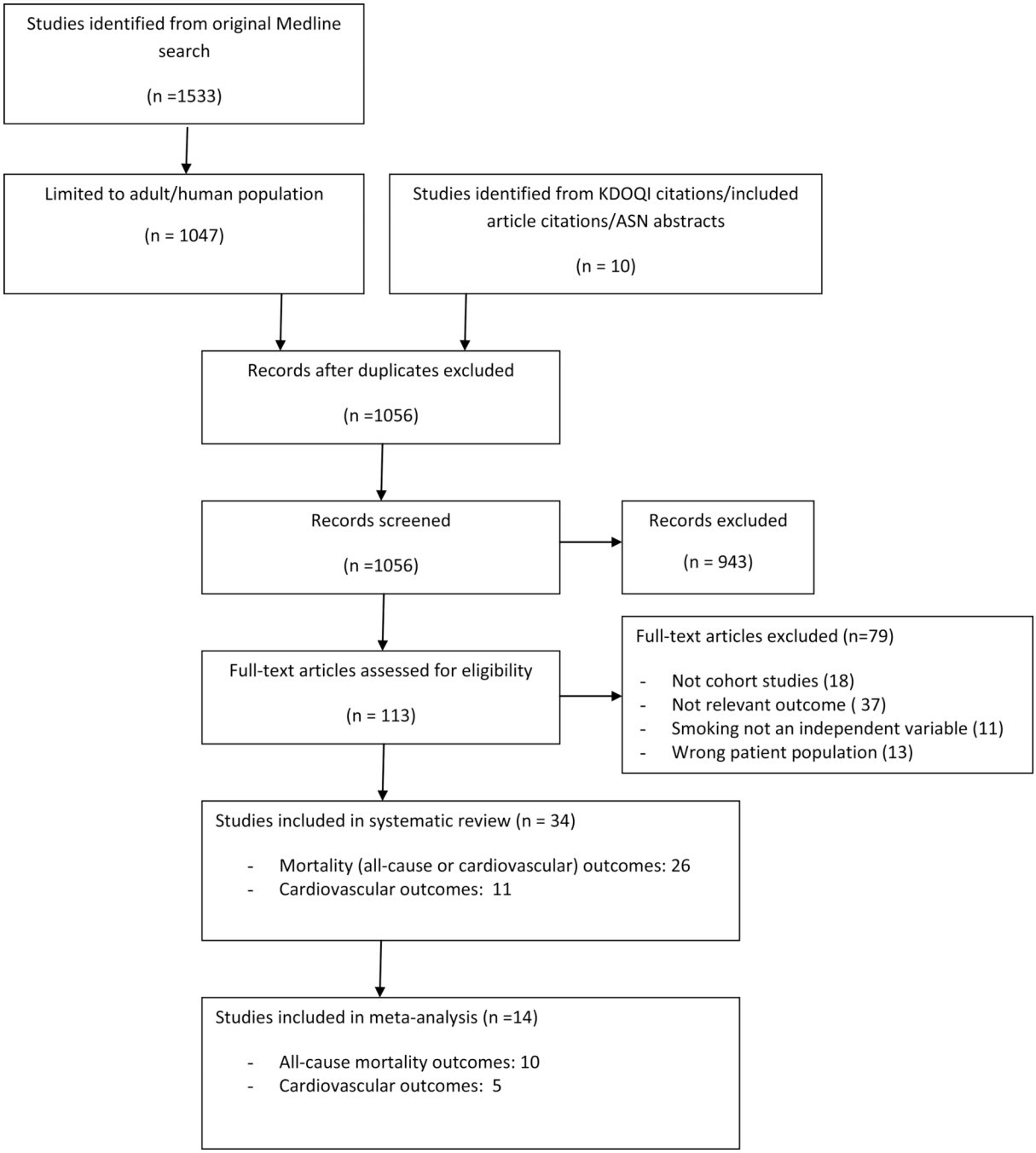

Figure 1.
Flow diagram for study selection

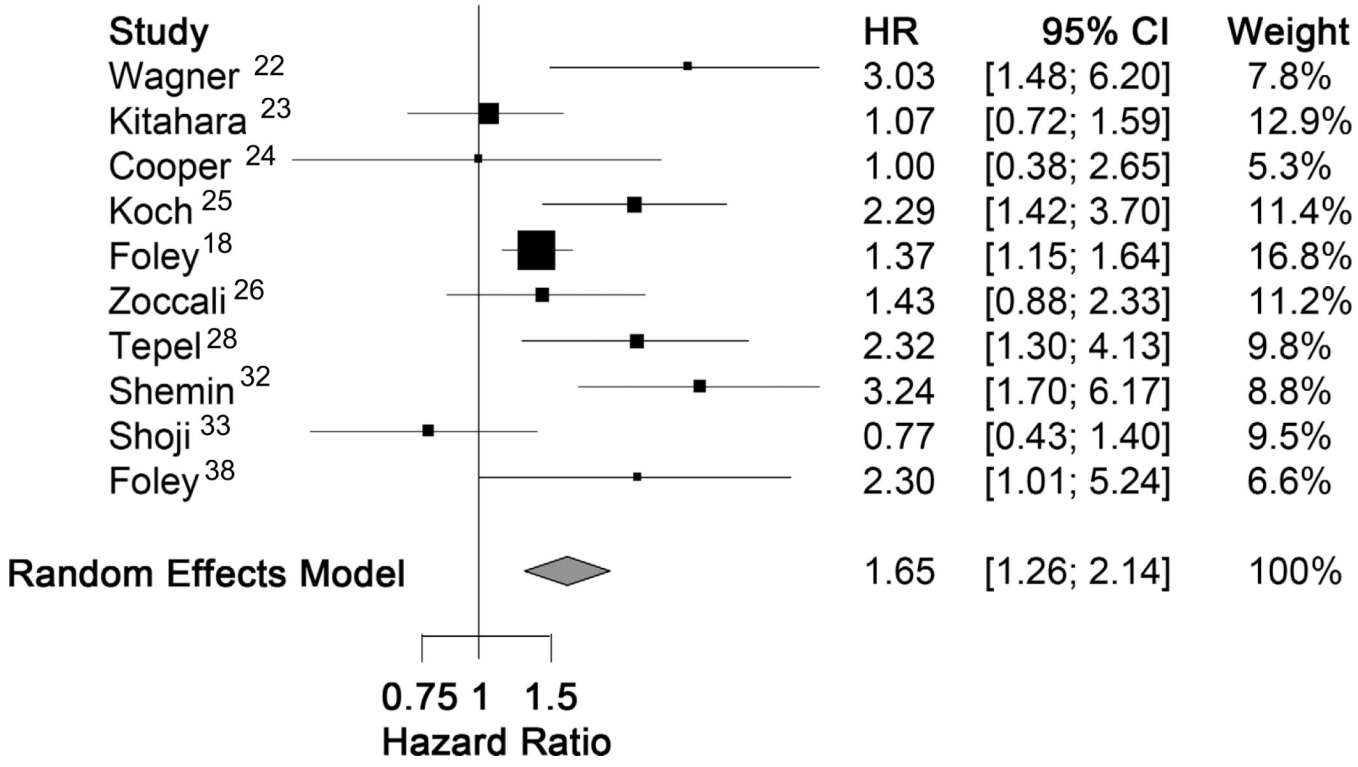

Figure 2.
Forest plot for all-cause mortality

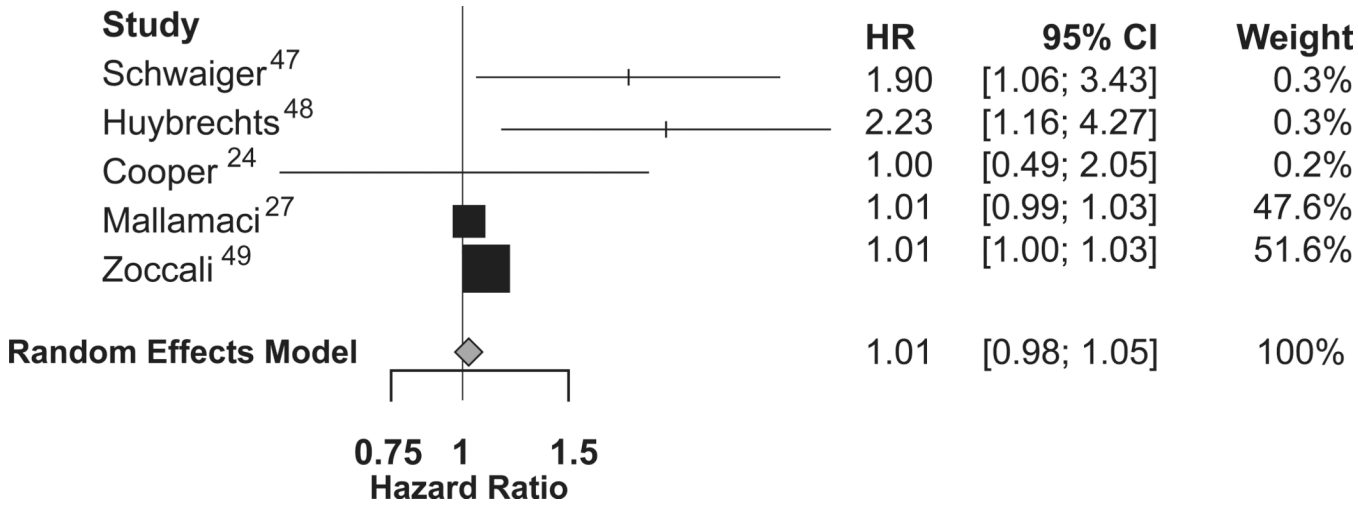

Figure 3.
Forest plot for incident cardiovascular events

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Table 1

Studies reporting mortality rates.

Reference	Included in meta-analysis?	Dialysis Modality (n)	Smoking definition	Mortality outcome	Association	Magnitude**	Notes
Terrier et al, 2008 19	N	HD (187)	Not specified	All-cause; CV	All-cause, no; CV, yes	All-cause: NA; CV: RR, 2.52	
Plantinga et al, 2007 20	N	HD (767); PD (274)	Current or former	All-cause	Partial (yes at 2 y, no at 4 y)		
Braatvedt et al, 2006 21	N	PD (1293)	Current or former	All-cause	Yes	RR, 1.22 (1.02 – 1.46) for current or former	Smoking is primary variable of interest
Wagner et al, 2006 22	Y	HD (154)	Not specified	All-cause	Yes	HR, 3.03 (1.48 – 6.19)	
Kitahara et al, 2005 23	Y	HD (785)	Current or former	All-cause	No		
Cooper et al, 2004 24	Y	HD (57); PD (52)	Current or former	All-cause	No		
Koch et al, 2004 25	Y	HD (322)	Not specified	All-cause	Yes	HR, 2.29	
Foley et al, 2003 18	Y	HD (2018); PD (1923)	Never, former (quit >1 y), former (quit < 1 y), or current	All-cause	Yes (current smoking only)	HR, 1.37 (1.15 – 1.64) for current smokers	Smoking is primary variable of interest
Zoccali et al, 2003 26	Y	HD (227)	Current	All-cause; CV	All-cause: no; CV: no		
Mallamaci et al, 2002 27	N	HD (175)	Current	CV	No		
Tepel et al, 2002 28	Y	HD (188)	Not specified	All-cause	Yes	HR, 2.32 (1.30–4.12)	
Benedetto et al, 200129	N	HD (91); PD (47)	Current	CV	No		
Fleischmann et al, 2001 30	N	HD (453)	Current, former, or lifetime nonsmoker	All-cause	No		
Haubitz et al, 2001 31	N	PD (34)	Not specified	All-cause	No		
Shemin et al, 2001 32	Y	HD (114)	Current	All-cause	Yes	HR, 3.24 (1.7–6.17)	
Shoji et al, 2001 33	Y	HD (265)	Not specified	All-cause; CV	All-cause: no; CV: no		
Blacher et al, 1999 34	N	HD (241)	Current or former	All-cause; CV	All-cause: no; CV: no		
Mazzuchi et al, 1999 35	N	HD (531)	Current or quit ≤ 5 y	All-cause	Unclear*		
Zimmerman et al, 1999 36	N	HD (280)	Not specified	All-cause; CV	All-cause: no; CV: no		
Blacher et al, 1998 37	N	HD (79)	Current or former	All-cause; CV	All-cause: no; CV: no		

Reference	Included in meta-analysis?	Dialysis Modality (n)	Smoking definition	Mortality outcome	Association	Magnitude**	Notes
Foley et al, 1997 38	Y	433 total – modality not specified	Current	All-cause (diabetic subgroup only)	Yes	HR, 2.3 (1.0–5.2)	Diabetic subgroup only
Bloembergen et al, 1996 39	N	HD (2479)	Current or former	All-cause	No		
Fishbane et al, 1996 40	N	HD (132)	Not specified	All-cause; CV	All-cause: no; CV: no		
Soucie et al, 1996 41	N	HD (12,240); PD (3005)	Not specified	All-cause (≤90 d of initiation)	Yes	OR, 1.3 (1.0 – 1.7)	
Brown et al, 1994 42	N	HD (84); PD (165); both (16)	> 3 cigarettes/d for > 3 y	CV	Yes	38% vs 26%	
Postorino et al, 2008 43	N	HD (537)	Current or former	All-cause	No		Abstract

Abbreviations: HD = hemodialysis, PD = peritoneal dialysis; CV, cardiovascular; NA, not applicable; HR, hazard ratio; RR, risk ratio;

*No reference group identified, so it is unclear whether this is a mortality harm or benefit with smoking.

**where applicable, 95% confidence interval is shown in parentheses

Table 2

Studies reporting incident cardiovascular events.

Reference	Included in meta-analysis?	Dialysis Modality (n)	Smoking Definition	Outcome Assessed	Association	Magnitude**
Sanchez-Perales et al, 2010 44	N	375 (HD); 84 (PD)	Not defined	CVA	No	
Combe et al, 2009 45	N	29,838 (HD)	Current/recent (quit < 1 y) or former (quit > 1 y)	PVD (peripheral amputation)	Yes for current/recent, no for former	HR, 1.33 (1.08 – 1.64)
Shah et al, 2008 46	N	193 (HD); 81 (PD)	Current or quit ≤ 1 y	Composite CV events	Yes	OR, 2.14 (1.02 – 4,42)
Schwaiger et al, 2006 47	Y	154 (HD)	Current or former	Composite CV events	Yes	HR, 1.90 (1.05 – 3.43)
Huybrechts et al, 2005 48	Y	179 (HD)	Current or former	Composite CV events	Yes	HR, 0.67 (non-smokers vs smokers)
Cooper et al, 2004 24	Y	109 (HD & PD)	Current or former	Composite CV events	No	
Foley et al, 2003 18	N	3941 (HD & PD)	Current, former (quit < 1 y), former (quit >1 y), or never	CHF; CHD; CVA; PVD	CHF: yes for current; CHD: no; CVA: no; PVD: yes for current	CHF: HR, 1.59 (1.16 – 2.17); CHD & CVA: NA; PVD: HR, 1.68 (1.27 – 2.22)
Mallamaci et al, 2002 27	Y	175 (HD)	Current	Composite CV events	No	
Zoccali et al, 2002 49	Y	228 (HD)	Not specified	Composite CV events	No	
Cressman et al, 1992 50	N	129 (HD)	Not specified	Composite CV events	No	

Abbreviations: HD = hemodialysis, PD = peritoneal dialysis, CV = cardiovascular, CVA = stroke, CHF = congestive heart failure, PVD = peripheral vascular disease, CHD = coronary heart disease; HR, hazard ratio; NA, not applicable; OR, odds ratio

** where applicable, 95% confidence interval is shown in parentheses