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The association between physical activity and renal cancer: systematic review and meta-analysis

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Background: Physical activity may decrease renal cancer risk by reducing obesity, blood pressure, insulin resistance, and lipid peroxidation. Despite plausible biologic mechanisms linking increased physical activity to decreased risk for renal cancer, few epidemiologic studies have been able to report a clear inverse association between physical activity and renal cancer, and no meta-analysis is available on the topic.

Methods: We searched the literature using PubMed and Web of Knowledge to identify published non-ecologic epidemiologic studies quantifying the relationship between physical activity and renal cancer risk in individuals without a cancer history. Following the PRISMA guidelines, we conducted a systematic review and meta-analysis, including information from 19 studies based on a total of 2 327 322 subjects and 10 756 cases. The methodologic quality of the studies was examined using a comprehensive scoring system.

Results: Comparing high *vs* low levels of physical activity, we observed an inverse association between physical activity and renal cancer risk (summary relative risk (RR) from random-effects meta-analysis = 0.88; 95% confidence interval (CI) = 0.79–0.97). Summarising risk estimates from high-quality studies strengthened the inverse association between physical activity and renal cancer risk (RR = 0.78; 95% CI = 0.66–0.92). Effect modification by adiposity, hypertension, type 2 diabetes, smoking, gender, or geographic region was not observed.

Conclusion: Our comprehensive meta-analysis provides strong support for an inverse relation of physical activity to renal cancer risk. Future high-quality studies are required to discern which specific types, intensities, frequencies, and durations of physical activity are needed for renal cancer risk reduction.

Renal cancer is one of the top 10 cancer sites in the United States and Europe. Each year, about 65 000 new cases are diagnosed in the United States (Howlader *et al*, 2012) and about 60 000 new cases are diagnosed in the European Union (Boyle and Ferlay, 2005). Well-established unfavourable risk factors for renal cancer include smoking, obesity, hypertension, and type 2 diabetes mellitus (Scelo and Brennan, 2007). In contrast, physical activity may prevent the development of renal cancer, partly because it helps reduce obesity (Wing, 1999), blood pressure (Blair *et al*, 1984), and insulin resistance (Rosenthal *et al*, 1983). Physical activity may also independently decrease renal cancer risk by lowering lipid peroxidation levels (Vincent *et al*, 2002). However, few available epidemiologic studies have been able to report a clear inverse association between physical activity and renal cancer (Leitzmann, 2011). Moreover, no meta-analysis is available on the relation between physical activity and renal cancer. To address this research gap, we conducted a systematic literature search and meta-analysis to quantify the association between physical activity and renal cancer, taking into account the methodologic quality of the studies.

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MATERIALS AND METHODS

Literature search. Our systematic review and meta-analysis adhered to the PRISMA guidelines (Moher *et al*, 2009). Both authors searched the literature using PubMed (see Appendix B for PubMed search options) and Web of Knowledge (see Appendix C for Web of Knowledge search options) to identify published non-ecologic epidemiologic studies quantifying the relationship between physical activity and renal cancer risk in individuals without a cancer history. That search was complemented by a scan of the reference lists of the identified studies and a scan of the reference list of a previous systematic review (Leitzmann, 2011). We considered all human research articles published in English through the end of September 2012 not classified as review, meta-analysis, editorial, comment, letter, practice guideline, or news. Our search strategy included the terms physical activity, exercise, cardiorespiratory fitness, cardiovascular fitness, resistance training, endurance training, aerobic, sport, athletes, players, lifestyle, kidney cancer, renal cancer, renal cell cancer, renal carcinoma, renal cell carcinoma, cancer, risk, incidence, and mortality. The search strategy excluded research on cancer survivors and research on specific types of cancer other than renal cancer. That search yielded 586 potential articles. Irrelevant articles were eliminated after screening titles and abstracts ($n=477$) or manuscripts ($n=82$). The 27 remaining studies (Goodman *et al*, 1986; Paffenbarger *et al*, 1987; Brownson *et al*, 1991; Lindblad *et al*, 1994; Mellemgaard *et al*, 1994, 1995; Bergstrom *et al*, 1999, 2001; Parker *et al*, 2002; Menezes *et al*, 2003; Mahabir *et al*, 2004; Nicodemus *et al*, 2004; van Dijk *et al*, 2004; Washio *et al*, 2005; Chiu *et al*, 2006; Pan *et al*, 2006; Setiawan *et al*, 2007; Tavani *et al*, 2007; Hu *et al*, 2008, 2009; Moore *et al*, 2008; Thompson *et al*, 2008; Yun *et al*, 2008; Spyridopoulos *et al*, 2009; Wilson *et al*, 2009; George *et al*, 2011; Parent *et al*, 2011) proved to be relevant.

To avoid duplicate information from overlapping studies, we removed eight of the 27 identified studies because their results were pooled (Lindblad *et al*, 1994; Mellemgaard *et al*, 1994) or updated (Parker *et al*, 2002; Menezes *et al*, 2003; Pan *et al*, 2006) in studies (Mellemgaard *et al*, 1995; Chiu *et al*, 2006; Hu *et al*, 2008) using the same database, because they reported results (Hu *et al*, 2009; Wilson *et al*, 2009) presented earlier (Mahabir *et al*, 2004; Hu *et al*, 2008), or because their investigations of total sitting time (George *et al*, 2011) were closely related to a previous study (Moore *et al*, 2008) on physical activity from the same cohort. The remaining 19 studies (Goodman *et al*, 1986; Paffenbarger *et al*, 1987; Brownson *et al*, 1991; Mellemgaard *et al*, 1995; Bergstrom *et al*, 1999, 2001; Mahabir *et al*, 2004; Nicodemus *et al*, 2004; van Dijk *et al*, 2004; Washio *et al*, 2005; Chiu *et al*, 2006; Setiawan *et al*, 2007; Tavani *et al*, 2007; Hu *et al*, 2008; Moore *et al*, 2008; Thompson *et al*, 2008; Yun *et al*, 2008; Spyridopoulos *et al*, 2009; Parent *et al*, 2011) were included in the meta-analysis.

Quality score. The magnitude and heterogeneity of risk estimates may depend on the methodologic quality associated with the underlying study and with the risk estimate derivation. Similar to three previous systematic reviews (Monninkhof *et al*, 2007; Voskuil *et al*, 2007; Liu *et al*, 2011) on the association between physical activity and specific types of cancer, both authors employed a quality score proposed by Voskuil *et al* (2007) to assess the methodologic quality of the studies and the consistency of the available evidence. Please refer to Appendix A for a description of the items covered by the quality score.

Main statistical analysis. Because some studies presented risk estimates for men and women and some studies investigated more than one physical activity domain, the 19 identified studies reported a total of 37 risk estimates. If separate risk estimates were available for men and women, both risk estimates were included in the meta-analysis because they were based on independent samples. To prevent potential bias arising from the fact that the risk estimates for the various physical activity domains were based on the same study population, both authors allowed only one estimate per study and gender in the main analysis. Specifically, if more than one physical activity domain was studied, we selected the risk estimate with the highest quality score in the main analysis. Of the 37 risk estimates, 25 were included in the main analysis.

In the meta-analysis, we interpreted odds ratios and hazard ratios as relative risk estimates (RR_i), computed the natural logarithms of those risk estimates $\log(RR_i)$ with corresponding standard errors $s_i = (\log(\text{upper 95\% confidence interval (CI) bound of RR}) - \log(RR))/1.96$, and employed a random-effects model to determine the weighted average of those $\log(RR_i)$s while allowing for heterogeneity of effects. In the random-effects model, the $\log(RR_i)$s were weighted by $w_i = 1/(s_i^2 + t^2)$ where s_i represented the standard error of $\log(RR_i)$ and t^2 represented the restricted maximum-likelihood estimate of the overall variance (Higgins and Thompson, 2002). In one case (Paffenbarger *et al*, 1987), we derived the standard error of the $\log(RR_i)$ using the *P*-value accompanying the RR estimate. In five additional cases (Brownson *et al*, 1991; Mellemgaard *et al*, 1995; Bergstrom *et al*, 1999, 2001; Chiu *et al*, 2006), the reported RRs used the highest rather than the lowest activity level as the reference category, so we reversed those RRs for comparability. Heterogeneity of the risk estimates was assessed using the Q- and I^2-statistics (Higgins and Thompson, 2002). Publication bias was tested using funnel plots (Egger *et al*, 1997), Egger's regression test (Egger *et al*, 1997), and Begg's rank correlation test (Begg and Mazumdar, 1994).

Statistical subanalyses. If a study presented separate risk estimates for recreational, occupational, and total physical activity, in a subanalysis all those risk estimates were included in the meta-analysis. Also, in a subanalysis we used all 37 risk estimates to investigate the impact of prespecified potentially influential methodologic factors on the summary risk estimate.

On the basis of pre-existing evidence, we hypothesised that the relations of physical activity to renal cell cancer would differ according to study design (cohort or case–control), physical activity domain (recreational, occupational, or total physical activity), and gender (men, women, or men and women combined). Thus, we conducted subanalyses within categories of those variables. We also performed exploratory analyses that were stratified by geographic region (North America, Europe, Asia), type of physical activity assessment (energy expenditure, physical fitness, moderate-to-vigorous physical activity duration, moderate-to-vigorous physical activity frequency, and qualitative assessments using categories, such as 'sedentary', 'light', 'moderate', or 'high' physical activity), timing in life of physical activity (recent physical activity, past physical activity, or consistent physical activity over time), number of adjustment factors (in quartiles), adjustments for smoking and obesity (adjusted for smoking and obesity, adjusted for smoking but not obesity, adjusted neither for smoking nor obesity; the option of adjusting for obesity but not smoking was not included because it did not occur), adjustment for hypertension (yes, no), adjustment for type 2 diabetes mellitus (yes, no), or methodologic quality score (in tertiles). To assess the influence of those factors, we applied random-effects meta-analysis regression comparing the model including the current factor of interest as a single explanatory variable with the null model not including any explanatory variables.

All statistical analyses were performed in R (R Development Core Team, 2011) using the R-package 'metafor' (Viechtbauer, 2010). Risk estimates are reported with 95% CIs. Statistical significance is based on the 5% significance level.

Table 1. Characteristics of the 19 studies on physical activity and renal cancer risk included in the meta-analysis

Authors, year, gender	Subjects	Cases	Region	Adjustment factors (excluding age, sex)	PA domain	Timing in life of PA	Relative risk (95% CI), high *vs* low PA	Low PA defined by	High PA defined by	Quality score (%)
Case–control studies										
Brownson *et al* (1991)										
Men	17 147	449	North America	Smoking	Occupational	Recent PA	**0.77 (0.50, 1.11)**	Low PA	High PA	45
Chiu *et al* (2006)										
Men	1660	225	North America	History of hypertension (yes/no), family history of renal cancer, marital status, red meat intake, proxy, SES (education), smoking, total energy intake, vegetable intake	Recreational	Consistent PA over time	**0.83 (0.48, 1.43)**	MVPA (10 min) less than once per month	MVPA (10 min) every day	76
Women	829	123			Recreational	Consistent PA over time	**0.40 (0.19, 0.83)**	MVPA (10 min) less than once per month	MVPA (10 min) every day	76
Goodman *et al* (1986)										
Men	378	189	North America	—	Recreational	Consistent PA over time	**1.14 (0.65, 2.05)**	None/occasional PA	Strenuous PA	66
					Occupational	Consistent PA over time	0.88 (0.48, 1.55)	None/occasional PA	Strenuous PA	62
Women	156	78			Recreational	Consistent PA over time	**1.11 (0.44, 2.97)**	None/occasional PA	Strenuous PA	66
					Occupational	Consistent PA over time	1.20 (0.41, 4.06)	None/occasional PA	Strenuous PA	62
Hu *et al* (2008)										
Men and women	6177	1138	North America	Residential area	Recreational	Recent PA	**0.90 (0.71, 1.14)**	No PA	55 min or more of MVPA per week	60
Mellemgaard *et al* (1995)										
Men	1994	864	Europe	Obesity (BMI), smoking, study centre	Recreational	Past PA	**1.11 (0.56, 2.50)**	Not physically active	Very active	62
					Occupational	Past PA	1.11 (0.71, 1.67)	Not physically active	Very active	58
Women	1308	572			Recreational	Past PA	**1.67 (0.71, 3.33)**	Not physically active	Very active	62
					Occupational	Past PA	1.67 (0.91, 3.33)	Not physically active	Very active	58
Parent *et al* (2011)										
Men	533	177	North America	Alcohol intake, coffee intake, obesity (BMI), proxy, race/ethnicity, recreational/ occupational activity (mutual adjustment), SES (socio-economic status, education), smoking	Total	Consistent PA over time	1.02 (0.70, 1.49)	Less than 1.5 MET at work independent of leisure time PA or 1.5–3.9 MET at work and less than once per week engaged in leisure time MVPA	Energy expenditure of 4 MET per day or more at work independent of leisure time PA or 1.6–3.9 MET per day at work and at least once per week engaged in leisure time MVPA	68
					Recreational	Past PA	**1.11 (0.76, 1.64)**	MVPA less than once per week	MVPA at least once per week	69
					Occupational	Consistent PA over time	0.84 (0.38, 1.89)	1.5 MET or less of energy expenditure	Energy expenditure of 4 MET or more per day	64

Table 1. (Continued)

Authors, year, gender	Subjects	Cases	Region	Adjustment factors (excluding age, sex)	PA domain	Timing in life of PA	Relative risk (95% CI), high *vs* low PA	Low PA defined by	High PA defined by	Quality score (%)
Spyridopoulos *et al* (2009) Men and women	350	70	Europe	Alcohol intake, coffee intake, history of diabetes (yes/no), obesity (serum adiponectin, serum leptin, waist–hip ratio), protein intake, SES (education), smoking, vegetarian diet	Recreational	Recent PA	**0.62 (0.48, 0.82)**	—	Increment of 3.5 h of MVPA per week	78
Tavani *et al*, 2007 Men and women	2301	767	Europe	Calendar year of interview, history of hypertension (yes/no), obesity (BMI), smoking, study centre	Recreational	Past PA	**1.03 (0.78, 1.36)**	Less than 2 h of MVPA per week	More than 7 h of MVPA per week	66
					Occupational	Past PA	0.71 (0.55, 0.92)	Low PA	High PA	55
Cohort studies										
Bergstrom *et al*, 1999 Men	674 025	2704	Europe	Calendar year of follow-up, residential area, SES (job title)	Occupational	Past PA	**0.80 (0.65, 0.98)**	Sedentary activities	High PA	58
Women	253 336	587			Occupational	Past PA	**1.25 (0.79, 1.96)**	Sedentary activities	High PA	58
Bergstrom *et al*, 2001 Men and women	17 241	102	Europe	History of hypertension (yes/no), obesity (BMI), smoking	Recreational	Consistent PA over time	**1.67 (0.83, 3.33)**	Sedentary activities	Strenuous PA	83
					Occupational	Consistent PA over time	1.25 (0.63, 2.50)	Sedentary activities	Strenuous PA	71
Mahabir *et al* (2004) Men	29 133	210	Europe	Alcohol intake, dietary fat intake, fruit and vegetable intake, history of hypertension (blood pressure), intervention group, recreational/ occupational activity (mutual adjustment), obesity (BMI), residential area, serum cholesterol, SES (education), smoking, total energy intake	Recreational	Recent PA	**0.46 (0.18, 1.13)**	Light PA	Heavy PA	75
					Occupational	Recent PA	1.08 (0.54, 2.15)	Sedentary activities	Heavy PA	63

Table 1. (Continued)

Authors, year, gender	Subjects	Cases	Region	Adjustment factors (excluding age, sex)	PA domain	Timing in life of PA	Relative risk (95% CI), high *vs* low PA	Low PA defined by	High PA defined by	Quality score (%)
Moore *et al* (2008)										
Men and women	482 386	1238	North America	Body height, history of diabetes (yes/no), history of hypertension (yes/no), obesity (BMI), protein intake, race/ethnicity, smoking.	Recreational	Recent PA	**0.77 (0.64, 0.92)**	Never/rarely engaging in VPA	Five times per week or more engaged in VPA (more than 20 min)	76
					Occupational	Recent PA	0.84 (0.57, 1.22)	Mostly sitting	Heavy PA	65
Nicodemus *et al* (2004)										
Women	34 637	124	North America	—	Recreational	Recent PA	**0.37 (0.14, 0.99)**	Low VPA frequency	High VPA frequency	71
Paffenbarger *et al* (1987)										
Men and women	56 683	53	North America	Birth year	Recreational	Past PA	**0.95 (0.47, 1.94)**	Less than 5 h of VPA per week	5 h of VPA per week or more	61
Setiawan *et al* (2007)										
Men	75 162	220	North America	Alcohol intake, history of hypertension (yes/no), obesity (BMI), smoking	Total	Recent PA	**1.09 (0.75, 1.58)**	1.4 MET per day or less	Energy expenditure of 1.8 MET per day or more	77
Women	85 964	127			Total	Recent PA	**0.66 (0.40, 1.10)**	1.4 MET per day or less	Energy expenditure of 1.8 MET per day or more	77
Thompson *et al* (2008)										
Men	21 663	31	North America	Alcohol intake, examination year, history of cancer, history of diabetes (fasting glucose level), obesity (BMI), smoking	Total	Recent PA	**0.91 (0.45, 2.68)**	Lowest physical fitness quintile	Upper two physical fitness quintiles	69
van Dijk *et al* (2004)										
Men	2335	179	Europe	Obesity (BMI), smoking, total energy intake	Recreational	Recent PA	**0.74 (0.44, 1.23)**	Less than 30 min of MVPA per day	More than 10.5 h of MVPA per week	77
					Occupational	Consistent PA over time	0.82 (0.46, 1.47)	Energy expenditure of $<8\,kJ\,min^{-1}$	Energy expenditure of $>12\,kJ\,min^{-1}$	76
Women	2444	96			Recreational	Recent PA	**1.13 (0.56, 2.29)**	Less than 30 min of MVPA per day	More than 10.5 h of MVPA per week	77
Washio *et al* (2005)										
Men and women	114 517	38	Asia	—	Recreational	Recent PA	**0.54 (0.25, 1.18)**	MVPA less than once per week	MVPA once per week or more	58
					Occupational	Recent PA	1.44 (0.72, 2.88)	Sedentary activities	Physically active	51
Yun *et al* (2008)										
Men	444 963	395	Asia	Alcohol intake, dietary pattern, history of diabetes (fasting glucose level), obesity (BMI), SES (employment), smoking	Recreational	Recent PA	**1.01 (0.83, 1.23)**	Combination of MVPA frequency and duration: MVPA less than 4 times per week and less than 30 min per session	Combination of MVPA frequency and duration: MVPA at least five times per week and at least 30 min per session	71

Abbreviations: BMI = body mass index; MET = metabolic equivalent of task; MVPA = moderate-to-vigorous physical activity; PA = physical activity; RR = relative risk; SES = socioeconomic status; VPA = vigorous physical activity. The 19 studies are grouped by study design. The main meta-analysis considered just one risk estimate (in bold) per study and gender.

Table 2. Summary risk estimates and I^2 measures of heterogeneity from random-effects models stratified by selected study characteristics

Stratification criterion	Number of included RRs	RR (95% CI) (high *vs* low PA) from random-effects model	I^2 (%)	*P*-value[a]
Methodologic quality[b]				
RRs within upper tertile of quality score	11	0.78 (0.66, 0.92)	33	
RRs within intermediate tertile of quality score	12	1.00 (0.89, 1.13)	0	
RRs within lower tertile of quality score	14	0.93 (0.80, 1.07)	30	0.02
PA assessment				
RRs based on qualitative PA assessments	18	0.98 (0.85, 1.14)	35	
RRs based on energy expenditure	6	0.97 (0.84, 1.12)	0	
RRs based on MVPA duration	6	0.85 (0.69, 1.04)	43	
RRs based on MVPA frequency	6	0.72 (0.53, 0.97)	53	0.24
PA domain				
RRs based on total activity	4	0.95 (0.76, 1.20)	0	
RRs based on occupational activity	14	0.91 (0.79, 1.04)	21	
RRs based on recreational activity	19	0.88 (0.77, 1.00)	40	0.84
Timing in life of PA				
RRs based on recent PA	16	0.83 (0.74, 0.93)	28	
RRs based on consistent PA over time	11	0.96 (0.79, 1.15)	0	
RRs based on past PA	10	1.01 (0.84, 1.20)	46	0.18
Gender				
RRs among men	17	0.93 (0.84, 1.02)	2	
RRs among women	9	0.95 (0.66, 1.36)	57	
RRs among men and women	11	0.85 (0.73, 0.98)	42	0.41
Study design				
RRs from case–control studies	18	0.91 (0.79, 1.04)	36	
RRs from cohort studies	19	0.89 (0.80, 0.99)	19	0.93
Study region				
RRs from studies in North America	18	0.85 (0.77, 0.94)	0	
RRs from studies in Europe	16	0.95 (0.80, 1.12)	51	
RRs from studies in Asia	3	1.00 (0.83, 1.20)	0	0.63
Number of adjustment factors[c]				
RRs within upper tertile of number of adjustment factors	12	0.83 (0.71, 0.97)	40	
RRs within intermediate tertile of number of adjustment factors	4	0.87 (0.68, 1.10)	52	
RRs within lower tertile of number of adjustment factors	21	0.96 (0.85, 1.08)	14	0.28
Adjustment for smoking and obesity				
RRs adjusted for smoking and obesity	23	0.92 (0.82, 1.03)	37	
RRs adjusted for smoking but not obesity	3	0.71 (0.54, 0.94)	0	
RRs adjusted neither for smoking nor obesity	11	0.89 (0.78, 1.01)	2	0.31
Adjustment for hypertension				
RRs adjusted for hypertension	12	0.85 (0.73, 0.97)	30	
RRs not adjusted for hypertension	25	0.93 (0.83, 1.03)	24	0.30
Adjustment for diabetes				
RRs adjusted for diabetes	5	0.81 (0.66, 0.99)	57	
RRs not adjusted for diabetes	32	0.92 (0.84, 1.01)	14	0.18

Abbreviations: CI = confidence interval; MVPA = moderate-to-vigorous physical activity; PA = physical activity; RR = relative risk.
[a]*P*-values for effect heterogeneity across strata were obtained from random-effects meta-regression comparing the model including the stratification variable as a single explanatory variable with the null model not including any explanatory variables.
[b]The quality scores ranged from 45 to 83 percentage points (out of 100 percentage points), with lower and upper tertile cutoffs of 62 percentage points and 71 percentage points, respectively.
[c]The number of adjustment factors (not counting adjustments for age and sex) ranged between 0 and 12, with lower and upper tertile cutoffs of 3 and 5, respectively.

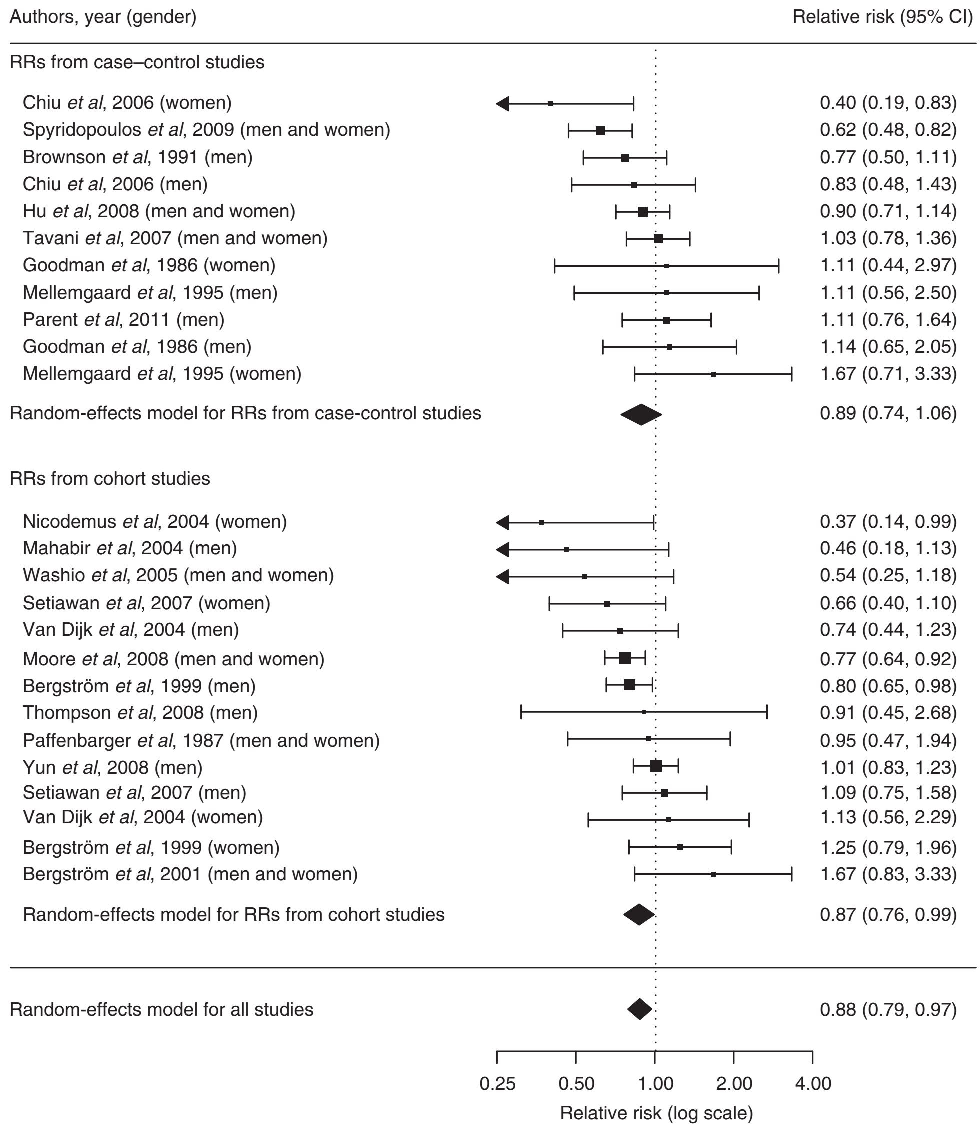

Figure 1. Forest plot corresponding to the main random-effects meta-analysis including 25 risk estimates quantifying the relationship between high physical activity and renal cancer risk. Relative risks (RRs) compare high *vs* low levels of physical activity and are grouped by study design. The size of the box representing each risk estimate is proportional to the weight that the risk estimate contributed to the summary risk estimate.

RESULTS

Description of underlying study characteristics. Table 1 presents the 19 studies on physical activity and renal cancer risk included in the meta-analysis. Because six studies stratified results by gender and nine studies investigated more than one physical activity domain, the 19 studies reported a total of 37 risk estimates.

When grouping studies by potentially effect modifying factors (Table 2), we noted that there was an equal number of risk estimates from case–control and prospective cohort studies, with the vast majority of studies originating in the United States or Europe. Half of the risk estimates were based on recreational physical activity, one-third of the risk estimates were based on occupational activity, and four risk estimates were based on total physical activity. Half of the physical activity assessments were of a qualitative type and the remaining half were of a quantitative type. Nearly two-thirds of the risk estimates were adjusted for smoking and obesity, one-third of the risk estimates were adjusted for hypertension, and one-sixth of the risk estimates were adjusted for history of type 2 diabetes mellitus.

Meta-analysis. The random-effects model summarising the 25 risk estimates with the highest quality scores from each of the 19 studies (Figure 1) revealed a statistically significant 12% reduction in renal cancer risk when comparing a high with a low level of physical activity (RR = 0.88; 95% CI = 0.79–0.97; $I^2 = 33\%$). The magnitude of that summary risk estimate did not materially change when grouping those 25 risk estimates by study design (Figure 1), physical activity domain (Figure 2), or gender (Figure 3). That meta-analysis combined a total of 2 327 322 subjects and 10 756 cases. No publication bias was indicated by the funnel plot (Figure 4), Egger's regression test ($P = 0.89$), or Begg's rank correlation test ($P = 0.53$).

Renal cancer end point. Because physical activity may differentially impact the incidence *vs* mortality of kidney cancer, we repeated the main analysis after excluding the two risk estimates from the papers on kidney cancer mortality (Washio *et al*, 2005; Thompson *et al*, 2008). The summary risk estimate remained unchanged (RR = 0.88; 95% CI = 0.80–0.98).

Potentially influential methodologic factors. In subanalyses investigating potentially influential methodologic factors, all 37

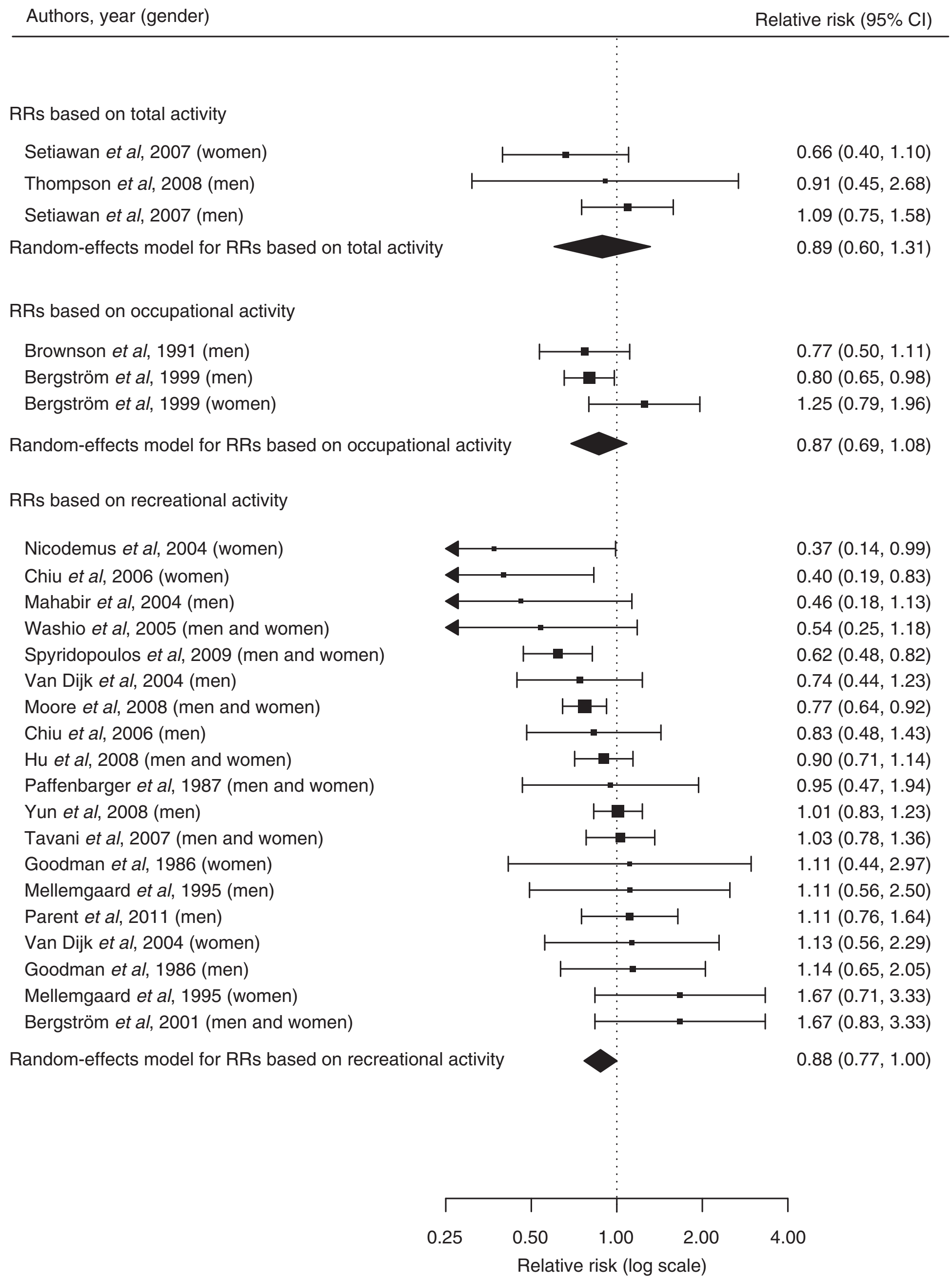

Figure 2. Forest plot corresponding to the main random-effects meta-analysis including 25 risk estimates quantifying the relationship between high physical activity and renal cancer risk. Relative risks (RRs) compare high *vs* low levels of physical activity and are grouped by physical activity domain. The size of the box representing each risk estimate is proportional to the weight that the risk estimate contributed to the summary risk estimate.

risk estimates were used. The random-effects summary risk estimate (RR = 0.90; 95% CI = 0.82–0.98; $I^2 = 26\%$) of those 37 risk estimates did not substantially differ from that of the main analysis. We found that the methodologic quality score significantly influenced the magnitude of the summary risk estimate ($P = 0.02$; Table 2) but not the underlying overall variation t^2. The best evidence synthesis of studies that fell into the high tertile of the quality score yielded a meta-analysis estimate for the relation of physical activity to renal cancer of 0.78 (95% CI = 0.66–0.92; $t^2 = 0.02$). In contrast, the meta-analysis RRs for studies falling into the intermediate (RR = 1.00; 95% CI = 0.89–1.13; $t^2 = 0$) and lower (RR = 0.93; 95% CI = 0.80–1.07; $t^2 = 0.02$) tertiles of the quality score were statistically nonsignificant.

When stratifying by the type of physical activity assessment, the summary risk estimates based on frequency of moderate-to-vigorous physical activity (RR = 0.72; 95% CI = 0.53–0.97) or duration of moderate-to-vigorous physical activity (RR = 0.85; 95% CI = 0.69–1.04) appeared to be stronger than those based on energy expenditure (RR = 0.97; 95% CI = 0.84–1.12) or qualitative physical activity assessments (RR = 0.98; 95% CI = 0.85–1.14). However, that variation was not statistically significant ($P = 0.24$). Similarly, the magnitude of the inverse association between physical activity and renal cancer appeared to be stronger with a larger number of adjustment factors, although that difference was not statistically significant ($P = 0.28$). The meta-analysis RR for studies in the top tertile of the number of adjustment factors was

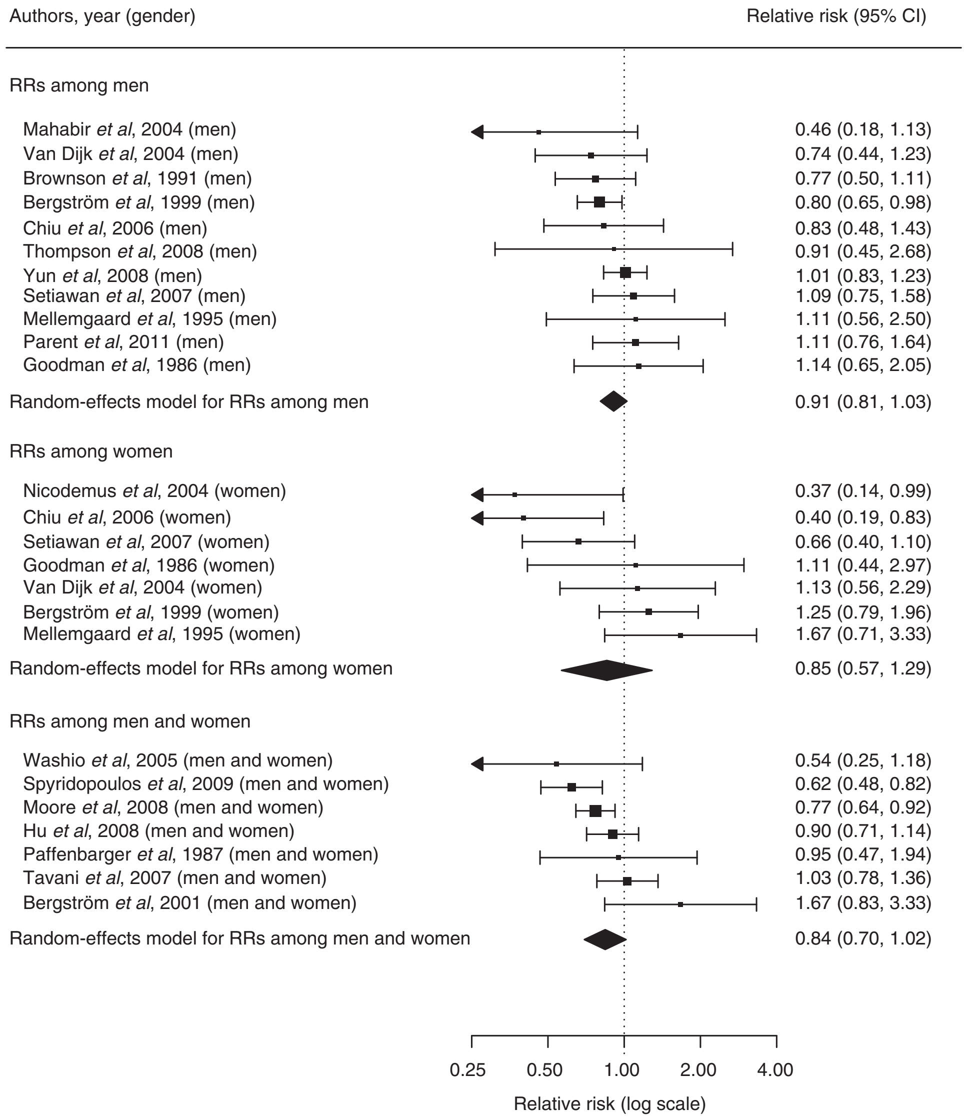

Figure 3. Forest plot corresponding to the main random-effects meta-analysis including 25 risk estimates quantifying the relationship between high physical activity and renal cancer risk. Relative risks (RRs) compare high *vs* low levels of physical activity and are grouped by gender. The size of the box representing each risk estimate is proportional to the weight that the risk estimate contributed to the summary risk estimate.

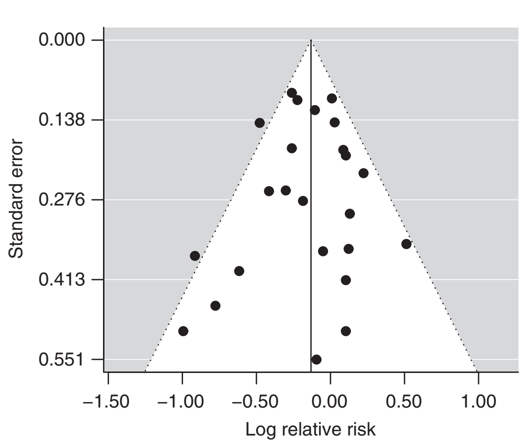

Figure 4. Funnel plot corresponding to the main random-effects meta-analysis including 25 risk estimates quantifying the relationship between high physical activity and renal cancer risk.

0.83 (95% CI = 0.71–0.97), whereas the RR for studies in the bottom tertile of the number of adjustment factors was 0.96 (95% CI = 0.85–1.08). There was no difference in risk estimates between study designs (RR for case–control studies = 0.91; 95% CI = 0.79–1.04; RR for cohort studies = 0.89; 95% CI = 0.80–0.99; *P*-value for interaction = 0.93). Similarly, none of the following remaining study characteristics affected the summary risk estimates: physical activity domain ($P = 0.84$), timing in life of physical activity ($P = 0.18$), gender ($P = 0.41$), geographic region ($P = 0.63$), joint adjustment for smoking and obesity ($P = 0.31$), hypertension adjustment ($P = 0.30$), and diabetes adjustment ($P = 0.18$).

We further examined study characteristics according to the quality score (Table 3). Studies that fell into the top tertile of the quality score tended to employ quantitative physical activity assessments, to investigate recreational activity, to examine recent physical activity, to use a cohort design, and to adjust for smoking, obesity, hypertension, and diabetes. In contrast, studies in the bottom tertile of the quality score tended to employ qualitative physical activity assessments, to investigate

Table 3. Distribution of methodologic characteristics (absolute frequencies) of all 37 risk estimates by tertile of quality score[a]

Methodologic characteristics	RRs within upper tertile of quality score	RRs within intermediate tertile of quality score	RRs within lower tertile of quality score
PA assessment			
RRs based on qualitative PA assessments	2	5	11
RRs based on energy expenditure	3	3	0
RR based on physical fitness	0	1	0
RRs based on MVPA duration	3	1	2
RRs based on MVPA frequency	3	2	1
PA domain			
RRs based on total activity	2	2	0
RRs based on occupational activity	1	4	9
RRs based on recreational activity	8	6	5
Timing in life of PA			
RRs based on recent PA	7	5	4
RRs based on consistent PA over time	4	5	2
RRs based on past PA	0	2	8
Gender			
RRs among men	5	7	5
RRs among women	3	2	4
RRs among men and women	3	3	5
Study design			
RRs from case-control studies	3	6	9
RRs from cohort studies	8	6	5
Study region			
RRs from studies in North America	5	8	5
RRs from studies in Europe	6	3	7
RRs from studies in Asia	0	1	2
Number of adjustment factors[b]			
RRs within upper tertile of number of adjustment factors	5	7	0
RRs within intermediate tertile of number of adjustment factors	2	1	1
RRs within lower tertile of number of adjustment factors	4	4	13
Adjustment for smoking and obesity			
RRs adjusted for smoking and obesity	9	9	5
RRs adjusted for smoking but not obesity	2	0	1
RRs adjusted neither for smoking nor obesity	0	3	8
Adjustment for hypertension			
RRs adjusted for hypertension	7	4	1
RRs not adjusted for hypertension	4	8	13
Adjustment for diabetes			
RRs adjusted for diabetes	2	3	0
RRs not adjusted for diabetes	9	9	14

Abbreviations: MVPA = moderate-to-vigorous physical activity; PA = physical activity; RR = relative risk.
[a]The quality scores ranged from 45 to 83 percentage points (out of 100 percentage points), with lower and upper tertile cutoffs of 62 percentage points and 71 percentage points, respectively.
[b]The number of adjustment factors (not counting adjustments for age and sex) ranged between 0 and 12, with lower and upper tertile cutoffs of 3 and 5, respectively.

occupational activity, to examine past physical activity, to use a case–control design, and to not adjust for smoking, obesity, hypertension, or diabetes.

After adjusting the main random-effects model for study quality (in tertiles), the previously observed heterogeneity (P-heterogeneity = 0.03) of risk estimates was no longer evident (P-heterogeneity = 0.12).

DISCUSSION

Main results. This comprehensive meta-analysis revealed a statistically significant 12% reduction in renal cancer risk associated with a high *vs* low level of physical activity.

Potentially influential factors. The summary RR estimate was not affected by individual potentially influential factors, such as type of physical activity assessment, physical activity domain, timing in life of physical activity, gender, study design, study region, number of adjustment factors, and adjustments for smoking, obesity, hypertension, or diabetes. However, the quality score representing a combination of specific factors affected the summary risk estimate. Summary risk estimates based on studies that fell into the top quality score tertile were statistically significantly inverse, whereas summary risk estimates based on studies that fell into the intermediate or bottom quality score tertiles were not. After adjusting for study quality, the previously observed heterogeneity in the random-effects model was no longer statistically significant.

The influence of individual factors was examined in previous meta-analyses of physical activity and cancers of the colorectum (Harriss *et al*, 2009; Boyle *et al*, 2012), pancreas (Bao and Michaud, 2008), and prostate (Liu *et al*, 2011). In agreement with our observations, no statistically significant heterogeneity across gender (Bao and Michaud, 2008; Boyle *et al*, 2012), study design (Liu *et al*, 2011), geographic region (Bao and Michaud, 2008; Harriss *et al*, 2009), physical activity domain (Boyle *et al*, 2012), or obesity adjustment (Bao and Michaud, 2008; Harriss *et al*, 2009) was reported.

The influence of a quality score combining several factors was previously studied with respect to the associations between physical activity and cancers of the breast (Monninkhof *et al*, 2007), endometrium (Voskuil *et al*, 2007), prostate (Liu *et al*, 2011), colon (Boyle *et al*, 2012), and pancreas (O'Rorke *et al*, 2010). In agreement with our findings, the meta-analysis on physical activity and breast cancer (Monninkhof *et al*, 2007) detected a more pronounced risk reduction with increased quality score, while the remaining analyses (Voskuil *et al*, 2007; O'Rorke *et al*, 2010; Liu *et al*, 2011; Boyle *et al*, 2012) did not detect any statistically significant association between quality score and summary risk estimates. Two reviews (O'Rorke *et al*, 2010; Boyle *et al*, 2012), however, described decreased variation in risk estimates with increasing quality score. No such observation was made in this study.

Potential biological mechanisms. A high level of physical activity has been shown to reduce adiposity (Wing, 1999), hypertension (Blair *et al*, 1984), insulin resistance (Rosenthal *et al*, 1983), circulating levels of insulin-like growth factor 1 (Eliakim *et al*, 1996, 1998), and lipid peroxidation (Vincent *et al*, 2002) – factors positively associated with the development of renal carcinoma (Kellerer *et al*, 1995; Chow *et al*, 2000; Gago-Dominguez *et al*, 2002; van Dijk *et al*, 2004; Vatten *et al*, 2007; Yuen *et al*, 2009). Further potential cancer preventing mechanisms include the beneficial effects of physical activity on chronic inflammation and immune function (McTiernan, 2008). It is hypothesised, however, that the effects of physical activity on chronic inflammation are mediated, in part, through avoidance of adiposity. The exact mechanisms linking physical activity to immune function related to tumour suppression have not yet been established, but it is thought that physical activity improves the number or the function of natural killer cells.

Strengths and limitations. This is the first meta-analysis of physical activity and renal cancer. It bears the strengths and limitations inherent in any meta-analysis combining results from studies with heterogeneous study designs (Greenland and O'Rourke, 2008). Particular strengths of the current meta-analysis are that it is based on an extensive systematic literature review, that it rigorously excluded duplicate information induced by overlapping studies, and that it combined information from 19 studies, including a total of 2 327 322 subjects and 10 756 cases. A further strength is that it is among the few meta-analyses of physical activity and a specific type of cancer to assess the heterogeneity of summary estimates by potentially influential factors underlying the RR estimates. The employed quality score addressed potential selection, misclassification, and confounding biases, and accounted for heterogeneity of the results. An inverse association between physical activity and renal cancer risk was observed in analyses including all risk estimates and in analyses including only risk estimates from high-quality studies. In addition, no publication bias was detected.

One limitation of this meta-analysis is the large variation in the underlying studies regarding their definitions of exposure to physical activity – ranging from 'physically very active' to '5 h of vigorous physical activity per week or more'. Similarly, the definitions of physical activity referent groups ranged from 'not physically active' to '<5 h of vigorous physical activity per week'. Such variation did not allow us to conduct stratified analyses according to comparable groups of exposed and non-exposed individuals. Thus, we were not able to identify the specific type, intensity, frequency, and duration of physical activity required to lower renal cancer risk.

Conclusion. In conclusion, our comprehensive meta-analysis provides strong support for an inverse relation of physical activity to the risk of renal cancer. On the basis of high-quality studies, physical activity may decrease the risk of renal cancer by 22%. Future research is required to discern which specific types, intensities, frequencies, and durations of physical activity are needed for renal cancer risk reduction. High-quality studies that employ standardised physical activity assessments and uniform definitions of physical activity are warranted.

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APPENDIX A

Description of quality score

To assess the methodologic quality of studies, we employed a quality score proposed by Voskuil *et al* (2007). The maximum score was 105. The score addressed selection bias (up to 42 points), misclassification bias (up to 42 points), and confounding bias (up to 21 points). Specifically, the score covered the following 19 items: (1) percentage lost to follow-up (cohort studies, up to 8 points)/ percentage response (case–control studies, up to 8 points); (2) difference between percentage response among cases and controls (case–control studies: up to 6 points; cohort studies: 10 points by default); (3) percentage incident cases with known incidence date (*vs* inclusion of prevalent/fatal cases with unknown incidence date: up to 7 points, independent of study design); (4) cases and controls from the same population (case–control studies: up to 10 points; cohort studies: 10 points by default); (5) same exclusion criteria for cases and controls (case–control studies: up to 7 points; cohort studies: 7 points by default); (6) complete list of recreational physical activities (up to 4 points independent of study design); (7) assessment of total physical activity (up to 4 points); (8) assessment of physical activity intensity and frequency or assessment of physical activity intensity and duration (up to 5 points); (9) source of physical activity information (proxy/self-administered questionnaire/interview) (up to 4 points); (10) definition of physical activity score provided (up to 2 points); (11) examination of past physical activity (up to 4 points); (12) examination of change in physical activity (up to 4 points); (13) use of a valid or reliable physical activity assessment (up to 2 points); (14) minimisation of recall bias (up to 7 points); (15) valid cancer diagnosis (up to 4 points); (16) exclusion of benign cases (up to 2 points); (17) statistical adjustment for potential confounding variables (up to 4 points); (18) comprehensive adjustment for potential confounding variables (up to 9 points); (19) mutual adjustment for recreational and occupational physical activity (up to 8 points). With respect to item 18, we considered the well-established (Scelo and Brennan, 2007) renal cancer risk factors, such as smoking, obesity, hypertension, and type 2 diabetes mellitus, and awarded points based on how many of those factors had been included in the model (0 points for 0 factors, 4 points for 1 or 2 factors, and 9 points for 3 or 4 factors).

APPENDIX B

PubMed search strategy

For the PubMed search, last performed on 30 September 2012, we pasted the following search terms all at once into the PubMed search command line:

(physical activity[title/abstract] OR exercise[title/abstract] OR cardiorespiratory fitness[title/abstract] OR cardiovascular fitness[title/abstract] OR resistance training[title/abstract] OR endurance training[title/abstract] OR aerobic[title/abstract] OR sport[title/abstract] OR athletes[title/abstract] OR players[title/abstract] OR lifestyle[title/abstract]) AND (kidney cancer[title] OR renal cancer[title] OR renal cell cancer[title] OR renal carcinoma[title] OR renal cell carcinoma[title] OR cancer[title])

NOT (lung*[title] NOT renal cancer[title] NOT renal cell cancer[title] NOT kidney cancer[title]) NOT (bronchial[title] NOT renal cancer[title] NOT renal cell cancer[title] NOT kidney cancer[title]) NOT (breast*[title] NOT renal cancer[title] NOT renal cell cancer[title] NOT kidney cancer[title]) NOT (mamma*[title] NOT renal cancer[title] NOT renal cell cancer[title] NOT kidney cancer[title]) NOT (ovar*[title] NOT renal cancer[title] NOT renal cell cancer[title] NOT kidney cancer[title]) NOT (endometr*[title] NOT renal cancer[title] NOT renal cell cancer[title] NOT kidney cancer[title]) NOT (uter*[title] NOT renal cancer[title] NOT renal cell cancer[title] NOT kidney cancer[title]) NOT (cervi*[title] NOT renal cancer[title] NOT renal cell cancer[title] NOT kidney cancer[title]) NOT (gynecolog*[title] NOT renal cancer[title] NOT renal cell cancer[title] NOT kidney cancer[title]) NOT (prostat*[title] NOT renal cancer[title] NOT renal cell cancer[title] NOT kidney cancer[title]) NOT (testic*[title] NOT renal cancer[title] NOT renal cell cancer[title] NOT kidney cancer[title]) NOT (urinary*[title] NOT renal cancer[title] NOT renal cell cancer[title] NOT kidney cancer[title]) NOT (bladder*[title] NOT renal cancer[title] NOT renal cell cancer[title] NOT kidney cancer[title]) NOT (urothelial*[title] NOT renal cancer[title] NOT renal cell cancer[title] NOT kidney cancer[title]) NOT (colon*[title] NOT renal cancer[title] NOT renal cell cancer[title] NOT kidney cancer[title]) NOT (rectal*[title] NOT renal cancer[title] NOT renal cell cancer[title] NOT kidney cancer[title]) NOT (colorectal*[title] NOT renal cancer[title] NOT renal cell cancer[title] NOT kidney cancer[title]) NOT (bowel*[title] NOT renal cancer[title] NOT renal cell cancer[title] NOT kidney cancer[title]) NOT (*digestive*[title] NOT renal cancer[title] NOT renal cell cancer[title] NOT kidney cancer[title]) NOT (gastric*[title] NOT renal cancer[title] NOT renal cell cancer[title] NOT kidney cancer[title]) NOT (stomach*[title] NOT renal cancer[title] NOT renal cell cancer[title] NOT kidney cancer[title]) NOT (oesophag*[title] NOT renal cancer[title] NOT renal cell cancer[title] NOT kidney cancer[title]) NOT (esophag*[title] NOT renal cancer[title] NOT renal cell cancer[title] NOT kidney cancer[title]) NOT (pancrea*[title] NOT renal cancer[title] NOT renal cell cancer[title] NOT kidney cancer[title]) NOT (tract*[title] NOT renal cancer[title] NOT renal cell cancer[title] NOT kidney cancer[title]) NOT (duct*[title] NOT renal cancer[title] NOT renal cell cancer[title] NOT kidney cancer[title]) NOT (tube*[title] NOT renal cancer[title] NOT renal cell cancer[title] NOT kidney cancer[title]) NOT (liver*[title] NOT renal cancer[title] NOT renal cell cancer[title] NOT kidney cancer[title]) NOT (hepato*[title] NOT renal cancer[title] NOT renal cell cancer[title] NOT kidney cancer[title]) NOT (gallbladder*[title] NOT renal cancer[title] NOT renal cell cancer[title] NOT kidney cancer[title]) NOT (oral*[title] NOT renal cancer[title] NOT renal cell cancer[title] NOT kidney cancer[title]) NOT (pharyn*[title] NOT renal cancer[title] NOT renal cell cancer[title] NOT kidney cancer[title]) NOT (nasopharyn*[title] NOT renal cancer[title] NOT renal cell cancer[title] NOT kidney cancer[title]) NOT (laryn*[title] NOT renal cancer[title] NOT renal cell cancer[title] NOT kidney cancer[title]) NOT (lymphoid*[title] NOT renal cancer[title] NOT renal cell cancer[title] NOT kidney cancer[title]) NOT (bone*[title] NOT renal cancer[title] NOT renal cell cancer[title] NOT kidney cancer[title]) NOT (head and neck*[title] NOT renal cancer[title] NOT renal cell cancer[title] NOT kidney cancer[title]) NOT (skin*[title] NOT renal cancer[title] NOT renal cell cancer[title] NOT kidney cancer[title]) NOT (melanoma*[title] NOT renal cancer[title] NOT renal cell cancer[title] NOT kidney cancer[title]) NOT (brain*[title] NOT renal cancer[title] NOT renal cell cancer[title] NOT kidney cancer[title]) NOT (thora*[title] NOT renal cancer[title] NOT renal cell cancer[title] NOT kidney cancer[title]) NOT (thyroid*[title] NOT renal cancer[title] NOT renal cell cancer[title] NOT kidney cancer[title]) NOT (squamous cell*[title] NOT renal cancer[title] NOT renal cell cancer[title] NOT kidney cancer[title]) NOT (basal cell*[title] NOT renal cancer[title] NOT renal cell cancer[title] NOT kidney cancer[title]) NOT (adenoma*[title] NOT renal cancer[title] NOT renal cell cancer[title] NOT kidney cancer[title]) NOT (multiple[title] NOT renal cancer[title] NOT renal cell cancer[title] NOT kidney cancer[title]) NOT (mouth[title] NOT renal cancer[title] NOT renal cell cancer[title] NOT kidney cancer[title])

AND (risk[title/abstract] OR incidence[title/abstract] OR mortality[title/abstract])

NOT (surviv*[title] OR prognosis*[title] OR quality of life*[-title] OR fatigue*[title] OR pallia*[title] OR cancer patient*[title] OR cancer care*[title] OR recurrence*[title] OR progression*[title] OR clinical outcome*[title] OR chemotherapy*[title] OR radiation*[title] OR radiotherapy*[title] OR rehabilitation*[title] OR recovery*[title] OR cancer diagnosis[title] OR cancer treatment[-title] OR cancer surgery[title] OR with cancer[title])

AND English[lang]

NOT (review[ptyp] OR meta-analysis[ptyp] OR editorial[ptyp] OR comment[ptyp] OR letter[ptyp] OR guideline[ptyp] OR news[ptyp]) AND humans[MeSH Terms]

APPENDIX C

Web of Knowledge search strategy

For the Web of Knowledge search, last performed on 30 September 2012, we specified the following search steps:

#STEP 1 SET LEMMATIZATION = OFF (ADJUST YOUR SEARCH SETTINGS)

#STEP 2 PUT THE FOLLOWING TERMS INTO TOPIC SEARCH

(physical activity OR exercise OR cardiorespiratory fitness OR cardiovascular fitness OR resistance training OR endurance training OR aerobic OR sport OR athletes OR players OR lifestyle) AND (kidney cancer OR renal cancer OR renal cell cancer OR renal carcinoma OR renal cell carcinoma OR cancer)

AND (risk OR incidence OR mortality)

#STEP 3 PUT THE FOLLOWING TERMS INTO TITLE SEARCH

(kidney cancer OR renal cancer OR renal cell cancer OR renal carcinoma OR renal cell carcinoma OR cancer) NOT (lung* NOT renal cancer NOT renal cell cancer NOT kidney cancer) NOT (bronchial NOT renal cancer NOT renal cell cancer NOT kidney cancer) NOT (breast* NOT renal cancer NOT renal cell cancer NOT kidney cancer) NOT (mamma* NOT renal cancer NOT renal cell cancer NOT kidney cancer) NOT (ovar* NOT renal cancer NOT renal cell cancer NOT kidney cancer) NOT (endometr* NOT renal cancer NOT renal cell cancer NOT kidney cancer) NOT (uter* NOT renal cancer NOT renal cell cancer NOT kidney cancer) NOT (cervi* NOT renal cancer NOT renal cell cancer NOT kidney cancer) NOT (gynecolog* NOT renal cancer NOT renal cell cancer NOT kidney cancer) NOT (prostat* NOT renal cancer NOT renal cell cancer NOT kidney cancer) NOT (testic* NOT renal cancer NOT renal cell cancer NOT kidney cancer) NOT (urinary* NOT renal cancer NOT renal cell cancer NOT kidney cancer) NOT (bladder* NOT renal cancer NOT renal cell cancer NOT kidney cancer) NOT (urothelial* NOT renal cancer NOT renal cell cancer NOT kidney cancer) NOT (colon* NOT renal cancer NOT renal cell cancer NOT kidney cancer) NOT (rectal* NOT renal cancer NOT renal cell cancer NOT kidney cancer) NOT (colorectal* NOT renal cancer NOT renal cell cancer NOT kidney cancer) NOT (bowel* NOT renal cancer NOT renal cell cancer NOT kidney cancer) NOT (*digestive* NOT renal cancer NOT renal cell cancer NOT kidney cancer) NOT (gastric* NOT renal cancer NOT renal cell cancer NOT kidney cancer) NOT (stomach* NOT renal cancer NOT renal cell cancer NOT kidney cancer) NOT (oesophag* NOT renal cancer NOT renal cell cancer NOT kidney cancer) NOT (esophag* NOT renal cancer NOT renal cell cancer NOT kidney cancer) NOT (pancrea* NOT renal cancer NOT renal cell cancer NOT kidney cancer) NOT (tract* NOT renal cancer NOT renal cell cancer NOT kidney cancer) NOT (duct* NOT renal cancer NOT renal cell cancer NOT kidney cancer) NOT (tube* NOT renal cancer NOT renal cell cancer NOT kidney cancer) NOT (liver* NOT renal cancer NOT renal cell cancer NOT kidney cancer) NOT (hepato* NOT renal cancer NOT renal cell cancer NOT kidney cancer) NOT (gallbladder* NOT renal cancer NOT renal cell cancer NOT kidney cancer) NOT (oral* NOT renal cancer NOT renal cell cancer NOT kidney cancer) NOT (pharyn* NOT renal cancer NOT renal cell cancer NOT kidney cancer) NOT (nasopharyn* NOT renal cancer NOT renal cell cancer NOT kidney cancer) NOT (laryn* NOT renal cancer NOT renal cell cancer NOT kidney cancer) NOT (lymphoid* NOT renal cancer NOT renal cell cancer NOT kidney cancer) NOT (bone* NOT renal cancer NOT renal cell cancer NOT kidney cancer) NOT (head and neck* NOT renal cancer NOT renal cell cancer NOT kidney cancer) NOT (skin* NOT renal cancer NOT renal cell cancer NOT kidney cancer) NOT (melanoma* NOT renal cancer NOT renal cell cancer NOT kidney cancer) NOT (brain* NOT renal cancer NOT renal cell cancer NOT kidney cancer) NOT (thora* NOT renal cancer NOT renal cell cancer NOT kidney cancer) NOT (thyroid* NOT renal cancer NOT renal cell cancer NOT kidney cancer) NOT (squamous cell* NOT renal cancer NOT renal cell cancer NOT kidney cancer) NOT (basal cell* NOT renal cancer NOT renal cell cancer NOT kidney cancer) NOT (adenoma* NOT renal cancer NOT renal cell cancer NOT kidney cancer) NOT (multiple NOT renal cancer NOT renal cell cancer NOT kidney cancer) NOT (mouth NOT renal cancer NOT renal cell cancer NOT kidney cancer)

NOT (surviv* OR prognosis* OR quality of life* OR fatigue* OR pallia* OR cancer patient* OR cancer care* OR recurrence* OR progression* OR clinical outcome* OR chemotherapy* OR radiation* OR radiotherapy* OR rehabilitation* OR recovery* OR cancer diagnosis OR cancer treatment OR cancer surgery OR with cancer)

#STEP 4 SET RESEARCH AREA TO PUBLIC ENVIRONMENTAL OCCUPATIONAL HEALTH

#STEP 5 EXCLUDE ALL DOCUMENT TYPES APART FROM ARTICLE

#STEP 6 SET LANGUAGE TO ENGLISH