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Non-steroidal Anti-inflammatory Drug use Not Associated with Erectile Dysfunction Risk: Results from the Prostate Cancer Prevention Trial

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Abstract

- To evaluate associations of NSAID use and risk of ED, considering indications for NSAID use.
- Data are from 4,726 men in the placebo arm of the Prostate Cancer Prevention Trial (PCPT) without evidence of ED at baseline.
- Incident ED was defined as mild/moderate (decrease in normal function) and severe (absence of function).
- Proportional hazards models were used to estimate covariate-adjusted associations of NSAID-related medical conditions and time-dependent NSAID use with ED risk.
- Arthritis (HR: 1.56), chronic musculoskeletal pain (HR: 1.35), general musculoskeletal complaints (HR:1.36), headaches (HR:1.44), sciatica (HR:1.50), and atherosclerotic disease (HR:1.60) were all significantly associated with increased risk of, mild/moderate ED, while only general musculoskeletal complaints (HR:1.22), headaches (HR:1.47) and atherosclerotic disease (HR:1.60) were associated with increased risk of severe ED.
- Non-aspirin NSAID use was associated with an increased risk of mild/moderate ED (HR: 1.16, p=0.02) and Aspirin use was associated with an increased risk of severe ED (HR: 1.16, p=0.03, respectively).
- Associations of NSAID use with ED risk were attenuated after controlling for indications of NSAID use.
- The modest associations of NSAID use with ED risk in this cohort were likely due to confounding indications of NSAID use. NSAID use was not associated with ED risk.

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Keywords

erectile dysfunction; sexual dysfunction; physiological; anti-inflammatory agents; non-steroidal; aspirin; ibuprofen

Introduction

Erectile Dysfunction (ED) is a common condition affecting 31–52% of men over 50 years of age (1–4). An estimated 470,000 men between the ages of 50–69 years will develop ED in the United States annually, costing approximately \$330 million dollars or \$15 billion if all affected men sought treatment (4, 5). In addition to older age, several risk factors for ED have been identified. Obesity, physical inactivity, smoking, alcohol consumption, and medical conditions including diabetes, hypertension and hypercholesterolemia are known risk factors for ED (2, 6, 7).

Low-grade inflammation is a common pathophysiologic process underlying many known risk factors for ED and may interfere with appropriate biochemical and neurotransmitter signaling required for normal erections (8–13). Known inflammatory medical conditions, such as arthritis, joint pain, muscle aches, and chronic musculoskeletal pain as well as atherosclerotic disease, have been associated with ED prevalence in small retrospective studies (14–19). For example, in population-based analyses of nearly 45,000 patients with rheumatoid arthritis (RA), Keller et al. found that men with RA were 67% more likely to have concomitant diagnosis of ED when adjusting for age, income, location, obesity, alcohol use, and various cardiovascular risk factors. In addition, several studies have suggested an association between high circulating levels of various pro-inflammatory markers including Tumor Necrosis Factor, Factor VII, Interleukin-6, C-reactive protein, vascular cell adhesion molecule, and intracellular adhesion molecule and prevalence of ED (8–12). Underlying inflammatory and endothelial dysfunction associated with atherosclerotic disease has also been linked with development of vasculogenic ED (15, 17).

Non-steroidal anti-inflammatory drug (NSAID) use is common among middle-aged and older men. Over 22% of men between 45–64 years and 39% of men >65 years report NSAID use in the last week (20). Given the anti-inflammatory properties of NSAIDs, there is an interest in the potential preventive role of NSAIDs in the development and progression of ED. Two prior studies have reported that NSAID use is associated with a potential increased risk of ED. In a large, cross-sectional study of 80,966 men, Gleason et al. reported a 22% and 38% increased prevalence of any ED and severe ED (never able to achieve or keep an erection), respectively, among regular NSAID users (>5 days/week) (21). In addition, Shiri et al. reported an 80% higher risk of ED (quite often difficulty getting or keeping an erection, or failure of intercourse) in a small prospective study of Finnish men who reported regular NSAID use (22). Given the pathophysiologic basis of chronic inflammation in the development and progression of ED, anti-inflammatory medications, including NSAIDs, should reduce ED risk. However, it is unclear whether or not NSAIDs themselves are associated with ED risk.

We examined whether NSAID use was associated with risk of ED using prospective data from the placebo arm of the Prostate Cancer Prevention Trial (PCPT). We hypothesize that NSAID use is associated with a decreased risk of ED and the positive relationship between NSAID use and ED risk observed in prior studies is potentially attributable to confounding by indications bias.

Patients and Methods

Study Population

Data from the PCPT (1993–2003), a randomized, placebo-controlled trial evaluating finasteride use for primary prevention of prostate cancer was used for these analyses (23). Briefly, between 1993 and 1997, 18,880 men aged 55 years or older with a normal digital rectal examination, a prostate specific antigen level less than 3 ng/mL, and no history of prostate cancer or severe lower urinary tract symptoms were randomized to receive finasteride (5 mg/day) or placebo. Participants were followed for up to 7 years. Because finasteride affects sexual function, these analyses were restricted to the 9,457 placebo arm participants (24). All participants signed written informed consent, and the Institutional Review Board of the Fred Hutchinson Cancer Research Center (Seattle, WA), which serves as the statistical center for the PCPT, approved this study.

Data Collection

Current medication use was assessed by interview at study entry using closed- (ex: Do you take aspirin?) and open-ended questions. At each follow-up contact (6-month and annual clinic visits and 3- and 9-month telephone contacts) participants were asked, “Have you started any new medications since we last talked with you?” For these analyses, NSAIDs included aspirin and other salicylates, ibuprofen, sulindac, meloxicam, meclofenamate, nabumetone, and selective COX-II inhibitors such as celecoxib.

History of medical conditions was recorded at study entry. At each subsequent contact, participants were asked about the diagnosis of several specific medical conditions, followed by the question, “have you had other significant medical problems?” In addition, if a participant reported any medication use during the interview, they were asked to specify the condition being treated. For these analyses, medical indications for NSAID use were grouped as “arthritis” (osteoarthritis, rheumatoid arthritis, arthralgia, or joint pain), “general musculoskeletal complaints” (muscular discomfort, pain or cramping, muscle strain, tendonitis, bursitis, repetitive motion injuries, or carpal tunnel syndrome), “headaches,” “sciatica” (pinched nerve or sciatica), and “atherosclerotic disease” (coronary artery disease, ischemic heart disease, cerebrovascular disease, arteriosclerosis, peripheral vascular disease, myocardial infarction, etc). The date when the condition was first reported indicated the start of the exposure.

During the PCPT, sexual function was assessed at each study contact (every 3 months) to assess possible side effects related to finasteride use. Sexual function was evaluated using both patient and clinician completed assessments. The patient-completed Sexual Activity Scale is a four-item questionnaire administered at baseline and each annual visit, which was

developed for the PCPT to assess sexual frequency and problems over the previous four weeks (25). Additionally, at baseline and at each participant contact, clinical research associates assessed ED through open-ended questions. For this study, mild/moderate ED was defined as “decrease in normal function or able with difficulty to achieve vaginal penetration” and severe was defined as “absence of function/no erections,” based on self-report. Men with any grade of ED at baseline (n=4,676) were excluded, leaving 4,781 eligible men.

Statistical Analyses

All analyses were based on the time between randomization and the first report of ED or censoring event. Non-cases were censored at the time of 1) prostate cancer diagnosis; 2) last recorded ED assessment; or 3) death, with a maximum time under study of 7 years. A sensitivity analysis excluding men with prostate surgery or transurethral resection of prostate (TURP) history at baseline and censoring men who reported these procedures during the PCPT was also performed. Separate models were used to examine aspirin use alone (ignoring non-aspirin NSAIDs), non-aspirin NSAID use alone (ignoring aspirin), and any NSAID use, to discern the impact of aspirin use for the prevention of atherosclerotic disease. Aspirin also possesses unique anti-thrombotic properties, beneficial for specific clinical applications such as the prevention of atherosclerotic events. The date of first reported use defined the start of exposure. When information on whether and when NSAID use stopped was unavailable, we assumed that exposure was continuous until the censoring date. Only NSAID use for more than 6 months before censoring date was considered an exposure.

Cox proportional hazards models with time-dependent exposure were used to calculate the relative hazards of incident ED associated with medical conditions and NSAID use. All proportional hazards models were adjusted for age (years; continuous), race/ethnicity (Caucasian, African-American, Other), smoking status (current, former/never), BMI (continuous), marital status (current, former/never), and history of diabetes (yes, no). Controlling for physical activity and sexual frequency did not affect the multivariable models; therefore, these covariates were not included in final models. For models of the association between NSAID use and ED risk, the potential effect of confounding by indication was examined using models controlling for medical indications (time-dependent) of NSAID use.

Of the 9,457 participants in the placebo arm of the PCPT, 4,676 men with any grade of ED and 55 men without available post-randomization and covariate data were excluded. These analyses were restricted to the remaining 4,726 men. All analyses were completed using SAS software, version 9.3 (SAS Institute Inc., Cary, North Carolina). A two-sided *P* value less than 0.05 was considered statistically significant.

Results

Distributions of participant characteristics at baseline and their unadjusted associations with ED risk are shown in Table 1. Participants were mostly Caucasian, non-smokers, overweight or obese, and married. The overall incidence of mild/moderate and severe ED was 18.3 and 3.3 per 1,000 person-years (py), respectively. Diabetic men and men 65 years or older had

the highest rates of ED (mild/moderate ED: 27.6 and 23.8 per 1,000 py; severe : 7.8 and 5.0 per 1,000 py, respectively). A total of 2,818 men (59.7%) reported NSAID use during the trial; 40.9% reported use at baseline and 18.8% initiated use post-baseline. For aspirin and non-aspirin NSAIDs, 39.0% and 2.9% reported use at baseline and 8.6% and 23.8% initiated use post-baseline, respectively. Only 13.8% reported using both aspirin and non-aspirin NSAIDs at any time during the trial.

Table 2 gives covariate-adjusted hazards ratios for associations of medical conditions for NSAID use with mild/moderate and severe ED. Medical conditions including arthritis, chronic musculoskeletal pain, general musculoskeletal pain, headaches, pinched nerve/sciatica and atherosclerotic disease were associated with a significant increased risk of mild/moderate ED ranging from 35% (HR: 1.35 (95% confidence interval (CI): 1.11, 1.65)) for chronic musculoskeletal pain to 60% (HR: 1.60 (95% CI: 1.42, 1.79)) for atherosclerotic disease. Only general musculoskeletal pain, headaches, and atherosclerotic disease were associated with a significant increased risk of severe ED (Table 2).

Table 3 gives covariate-adjusted hazards ratios for associations of NSAID use with mild/moderate and severe ED. Reported results were adjusted for age, race, BMI, diabetes, marital status, smoking and status (Model 1) and also for medical indications for NSAID use (Model 2). In Model 1, non-aspirin NSAID use was associated with a modest but statistically significant 16% increase in risk of mild/moderate ED (Table 3). Aspirin was associated with a 16% increased risk of severe ED. Similar associations were found for total NSAID and aspirin use with mild/moderate ED risk and for total NSAID and non-aspirin NSAID use with severe ED risk, although these associations did not reach statistical significance. When medical indications for NSAID use were added as covariates to our statistical models (Model 2), the associations of time-dependent NSAID use were no longer statistically significant for non-aspirin NSAID use with mild/moderate ED and aspirin use and severe ED (Table 3). Sensitivity analysis excluding men who reported prostate surgery or TURP at baseline and censoring men who received these procedures during the trial showed similar findings and have not been shown.

Discussion

In this large, prospective study of men in the placebo arm of the PCPT, we found no evidence to suggest that NSAID use was associated with a reduced risk of incident ED. Instead, non-aspirin NSAID and aspirin use were associated with a statistically significant 16% and 16% increased risk of mild/moderate ED and severe ED, respectively. However, statistical models that, to the best of our abilities, control for medical indications of NSAID use suggest that the associations of non-aspirin NSAID and aspirin use with risk of ED may not be causal.

Confounding by indication bias is seen in pharmacoepidemiologic studies where indications for medication use are also associated with the disease under investigation (26, 27). This bias was encountered in our study and previous studies evaluating NSAIDs and ED risk. We controlled for confounding by indication bias by adding medical indications (for NSAID use) as covariates to our statistical models. The absolute difference in hazards ratios, by

adding these medical indications as covariates, was small. For example, the hazard ratio for non-aspirin NSAID use with mild/moderate ED was reduced from 1.16 ($P=0.02$) to 1.00 ($P=0.99$) and no longer statistically significant. Meanwhile, the hazard ratio for aspirin use and severe ED was reduced from 1.16 ($P=0.03$) to 1.10 ($P=0.16$) and was also no longer statistically significant.

We found that many common medical conditions that are indications for NSAID use were associated with ED risk. Previous studies have assessed the association of inflammatory medical conditions, such as arthritis, joint pain, muscle aches, and chronic musculoskeletal pain as well as atherosclerotic disease, with ED prevalence overall, although no prior studies have evaluated whether these associations differ by severity of ED (14–19). In population-based analyses of nearly 45,000 patients with rheumatoid arthritis (RA), Keller et al. found that men with RA were 67% more likely to have concomitant diagnosis of ED when adjusting for age, income, location, obesity, alcohol use, and various cardiovascular risk factors. In our study, arthritis, chronic and general musculoskeletal pain, headaches, pinched nerve or sciatica, and atherosclerotic disease were each associated with an increased risk of mild/moderate ED, but only general musculoskeletal complaints, headaches, atherosclerotic disease were associated with risk of severe ED. Underlying inflammatory and endothelial dysfunction associated with atherosclerotic disease has also been linked with development of vasculogenic ED (15, 17). There is evidence to suggest that vasculogenic ED associated with atherosclerotic disease is more likely to produce more severe ED symptoms that is consistent with our findings (15). The differences in associations of medical conditions with mild/moderate and severe ED may suggest different etiologies of less and more severe ED.

Two previous studies have examined associations of NSAID use and ED risk, although differences in population and study design limit comparison with our study. In a large cross-sectional study of 80,966 men, Gleason et al. found that NSAID use was higher among men who reported ED symptoms (self-report of sometimes or never being able to achieve and keep an erection rigid enough for sexual activity) when compared to men who reported no ED symptoms (odds ratio (OR):1.22) (21). Although their statistical models did adjust for common indications of low dose aspirin use (peripheral vascular disease and history of myocardial infarction), the small observed increase in risk could be due to uncontrolled confounding by other common indications of aspirin/NSAID use such as arthritis or chronic musculoskeletal pain. In a small prospective Finnish study, Shiri et al. reported that men who used NSAIDs at baseline had an 80% increased risk of subsequent ED, defined as self-reported difficulty in getting and/or maintaining an erection for intercourse (relative risk (RR): 1.8; 95% CI: 1.2, 2.6) (22). In this study only men who used NSAIDs at baseline were considered exposed, and although the authors attempted to control for confounding by indication, only history of arthritis at baseline, which was not associated with ED risk (RR: 1.3; 95% CI: 0.9, 1.8) was considered an indication for NSAID use. The fact that the associations of NSAID use and ED risk were similar among men who did (RR: 2.0; 95% CI: 1.2, 3.5) and did not (RR: 1.9; 95% CI: 1.2, 3.1) have arthritis suggests that these associations remain confounded by other medical indications (aside from arthritis) for NSAID use.

There are several strengths of this study that deserve mention. The careful assessment of incident ED is a principle strength. Given the known effects of finasteride on sexual function, extensive data on erectile function was collected at each patient contact (4 times/year) via medical evaluation and/or symptom assessment by clinical research associates as well as through the self-administered Sexual Activity Scale (25). Second, data on medication use were collected throughout the study (4 times/year) rather than at baseline alone, so we could capture NSAID use initiated post-baseline and evaluate associations of NSAID use with ED risk using time-dependent exposures. Third, we identified and controlled for medical conditions that were associated with both NSAID use and ED risk, and at least partly controlled for confounding by indication. Fourth, the PCPT was largely conducted prior to the approval of sildenafil; therefore, the effect of this medication on self-reported ED is likely minimal. Lastly, many characteristics of the PCPT, including the large sample size and the emphasis on capturing adverse sexual effects, contributed to the quality of data used in these analyses

We also acknowledge several limitations of this study. First, we only captured initiation of NSAID use and assumed continued usage thereafter. This would be a reasonable assumption for chronic NSAID use, but may not be accurate for acute NSAID use. Second, we did not capture data on NSAID dosing and therefore cannot evaluate potential dose-dependent associations of NSAID use with ED risk. The hypothesized association between NSAID use and ED risk may be dose-dependent as noted by Gleason et al (21). Third, with the exception of aspirin use, the collection of information on NSAID use and medical conditions was unstructured (open-ended questions) and thus is subject to omission and error. Fourth, because incident ED was defined based on the first report of symptoms, transient elevations in ED symptoms may have been misclassified as true. However, if present, this misclassification would be non-differential and the bias results towards the null. Fifth, given the small number of severe ED events we have limited power to detect associations of this endpoint with NSAID use. Finally, there are limits to the generalizability of this study, as most participants in the PCPT were healthy and well-educated men and may not represent the racial/ethnic, social, and health-related characteristics of American men overall. Future studies should specifically address frequency, duration, and dosing of NSAID use and the impact on ED risk in a large representative sample of men.

In conclusion, we found no evidence that use of NSAIDs reduces the risk of ED. We observed a slight increased risk of ED with non-aspirin NSAIDs and aspirin use; however these associations could largely be explained by confounding by indication bias. Medical conditions associated with NSAID use including arthritis, chronic and general musculoskeletal pain, headaches, pinched nerve or sciatica, and atherosclerotic disease were each associated with an increased risk of mild/moderate ED, but only general musculoskeletal complaints, headaches, atherosclerotic disease were associated with risk of severe ED. These findings are consistent with other evidence suggesting an association of ED with chronic inflammatory or chronic pain conditions and atherosclerotic disease (14–19). Our results suggest that NSAID use is not associated with the development of ED. Although these findings are unlikely to alter clinical practice, our results expand our understanding of etiology and progression of ED and establish a foundation for future studies.

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Distributions of baseline characteristics and their associations with rate of ED, Prostate Cancer Prevention Trial, 1993–2003

Table 1

	Total n	%	No. Mild/Moderate ED Events (%)	Person- Years	Rate ^a	No. Severe ED Events (%)	Person- Years	Rate ^a
Total	4726	100	3074 (65%)	16,831	18.3	905 (19%)	27,234	3.3
Age (years)								
55–59	1,860	39.4	1,084 (58%)	7,388	14.7	255 (14%)	11,258	2.3
60–64	1,496	31.7	995 (67%)	5,265	18.9	284 (19%)	8,619	3.3
65–69	1,370	29.0	995 (73%)	4,178	23.8	366 (27%)	7,357	5.0
Race								
Caucasian	4,375	92.6	2,843 (65%)	15,720	18.1	833 (19%)	25,301	3.3
African-American	171	3.6	112 (65%)	541	20.7	33 (19%)	936	3.5
Other	180	3.8	119 (66%)	570	20.9	39 (21%)	996	3.9
Smoking Status ^b								
Current	342	7.3	222 (65%)	1,116	19.9	66 (19%)	1,878	3.5
Former	2,694	57.0	1,815 (67%)	9,343	19.4	546 (21%)	15,476	3.5
Never	1,690	35.8	1,037 (61%)	6,372	16.3	293 (17%)	9,879	3.0
Body Mass Index ^c								
Normal (<25)	1,289	27.3	807 (63%)	4,808	16.8	205 (16%)	7,641	2.7
Overweight (25–29.9)	2,418	51.1	1,582 (65%)	8,654	18.3	472 (20%)	13,846	3.4
Obese (≥ 30)	1,019	21.6	685 (67%)	3,370	20.3	228 (22%)	5,746	4.0
Physical Activity ^b								
Sedentary	743	15.7	514 (69%)	2,492	20.6	168 (23%)	4,200	4.0

	Total n	%	No. Mild/Moderate ED Events (%)	Person- Years	Rate ^a	No. Severe ED Events (%)	Person- Years	Rate ^a
Light activity	1,986	42.0	1316 (66%)	6,915	19.0	379 (19%)	11,459	3.3
Moderate activity	1,490	31.5	941 (63%)	5,449	17.3	269 (18%)	8,564	3.1
Very active	485	10.3	288 (59%)	1,910	15.1	87 (18%)	2,882	3.0
Marital Status								
Currently married	4,037	85.4	2,644 (65%)	14,422	18.3	788 (20%)	23,437	3.4
Formerly married	553	11.7	353 (64%)	1,857	19.0	104 (19%)	3,007	3.5
Never married	136	2.9	77 (57%)	553	13.9	13 (10%)	788	1.6
Education Status								
High school or less	778	16.6	506 (65%)	2,716	18.6	179 (23%)	4,298	4.2
Some college	1,333	28.2	882 (66%)	4,668	18.9	459 (34%)	15,327	3.5
College grade	2,611	55.2	1,685 (65%)	9,443	17.8	267 (10%)	7,603	3.0
Diabetes								
Yes	152	3.2	116 (76%)	421	27.6	60 (40%)	765	7.8
No	4,574	96.8	2,958 (65%)	16,411	18.0	845 (18%)	26,468	3.2

^a per 1,000 person-years

^b Column person-years do not sum to total person-years due to missing values

^c Weight (kg)/height (m)²

Table 2

Associations of medical conditions with ED risk

		Mild/moderate Erectile Dysfunction					Severe Erectile Dysfunction				
		ED Events	Person- years	HR*	95% CI	P	ED Events	Person- years	HR*	95% CI	P
Arthritis	Yes	183	1,555	1.56	1.34–1.82	<.0001	37	1,456	1.20	0.95–1.52	0.13
	No	2,891	15,277	1.00			205	5,294	1.00		
Chronic musculoskeletal pain	Yes	104	1,179	1.35	1.11–1.65	0.003	26	1,040	1.22	0.91–1.64	0.18
	No	2,970	15,652	1.00			216	5,709	1.00		
General musculoskeletal complaints	Yes	369	3,414	1.36	1.21–1.52	<.0001	157	6,551	1.22	1.02–1.45	0.028
	No	2,705	15,168	1.00			85	2,898	1.00		
Headaches	Yes	325	2,434	1.41	1.25–1.58	<.0001	39	1,650	1.47	1.22–1.77	<.0001
	No	2,749	14,398	1.00			203	5,100	1.00		
Pinched Nerve/Sciatica	Yes	34	308	1.50	1.07–2.10	0.020	8	309	1.57	0.98–2.51	0.06
	No	3,040	16,524	1.00			234	6,442	1.00		
Atherosclerotic Disease	Yes	364	3,072	1.60	1.42–1.79	<.0001	55	1,851	1.60	1.35–1.89	<.0001
	No	2,710	13,759	1.00			187	4,898	1.00		

* Adjusted for age (continuous), race (Caucasian, other), BMI (continuous), diabetes, marital status (current, former, never), smoking status (current, former/never)

Table 3

Associations of NSAID use with ED risk, Prostate Cancer Prevention Trial, 1993–2003

	ED Events	Person- years	Model 1 ^a			Model 2 ^b			
			HR	95% CI	P	HR	95% CI	P	
Mild/moderate Erectile dysfunction									
NSAID use ^c	Yes	1,363	9,124	1.06	0.99, 1.15	0.12	1.01	0.93, 1.09	0.86
	No	1,711	7,707	1.00			1.00		
Aspirin use ^c	Yes	1,189	7,445	1.02	0.95, 1.10	0.56	0.99	0.92, 1.07	0.99
	No	1,885	9,387	1.00			1.00		
Non-aspirin NSAID use ^c	Yes	303	3,325	1.16	1.02, 1.31	0.02	1.00	0.88, 1.14	0.99
	No	2,771	13,507	1.00			1.00		
Severe Erectile dysfunction									
NSAID use ^c	Yes	482	15,892	1.11	0.97, 1.27	0.12	1.01	0.82, 1.24	0.24
	No	423	11,341	1.00			1.00		
Aspirin use ^c	Yes	426	12,627	1.16	1.02, 1.33	0.03	1.10	0.96, 1.26	0.16
	No	479	14,606	1.00			1.00		
Non-aspirin NSAID use ^c	Yes	133	6,717	1.09	0.90, 1.32	0.37	1.01	0.83, 1.23	0.90
	No	772	20,516	1.00			1.00		

NSAID: Non-steroidal anti-inflammatory drug; ED: Erectile dysfunction

^a . Model 1: Adjusted for age (continuous), race (Caucasian, other), BMI (continuous), diabetes, marital status (current, former, never), smoking status (current, former/never);^b . Model 2: Also adjusted for medical conditions: Grade 1 ED adjusted for arthritis, general musculoskeletal pain, chronic musculoskeletal pain, headaches, sciatica and atherosclerotic disease; Grade 3 ED adjusted for headaches, general musculoskeletal pain and atherosclerotic disease