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Does vitamin D deficiency contribute to erectile dysfunction?

Marc B. Sorenson[1,*] and William B. Grant[2]

[1]Sunlight Institute; Saint George, UT USA; [2]Sunlight, Nutrition, and Health Research Center; San Francisco, CA USA

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Abbreviations: CAM, cellular adhesion molecules; 95% CI, 95% confidence interval; CRP, C-reactive protein; CVD, cardiovascular disease; DM, diabetes mellitus; ED, erectile dysfunction; END, endothelial dysfunction; NO, nitric oxide; NOS, nitric oxide synthases; PAD, peripheral arterial disease; UVB, ultraviolet-B; VDD, vitamin D deficiency

Erectile dysfunction (ED) is a multifactorial disease, and its causes can be neurogenic, psychogenic, hormonal and vascular. ED is often an important indicator of cardiovascular disease (CVD) and a powerful early marker for asymptomatic CVD. Erection is a vascular event, and ED is often a vascular disease caused by endothelial damage and subsequent inhibition of vasodilation. We show here that risk factors associated with a higher CVD risk also associate with a higher ED risk. Such factors include diabetes mellitus, hypertension, arterial calcification and Inflammation in the vascular endothelium. Vitamin D deficiency is one of several dynamics that associates with increased CVD risk, but to our knowledge, it has not been studied as a possible contributor to ED. Here we examine research linking ED and CVD and discuss how vitamin D influences CVD and its classic risk factors—factors that also associate to increased ED risk. We also summarize research indicating that vitamin D associates with reduced risk of several nonvascular contributing factors for ED. We conclude that VDD contributes to ED. This hypothesis should be tested through observational and intervention studies.

Introduction: Important Facts Pertaining to this Discussion

Vitamin D is a steroid hormone produced in human skin by sunlight stimulation, specifically the ultraviolet-B (UVB) portion of the sunlight spectrum; about 80% of vitamin D is thus obtained.[1] The angle of sunlight varies greatly by season. In summer, the sun is overhead at noon, but in winter it stays closer to the horizon, and sunlight must pass through more atmosphere, which filters out much or all of the UVB. Therefore, availability of UVB exposure, and its resultant vitamin D production in skin, is highest in late spring through early fall and lowest from late fall through early spring. Consequently, vitamin D levels in the bloodstream also vary by season, with levels highest in late spring through early fall and lowest from late fall through early spring. For example, vitamin D levels in the UK are about 50% higher at the end of summer than at the end of winter.[1]

*Correspondence to: Marc B. Sorenson; Email: megamarc1@aol.com
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Vitamin D deficiency (VDD) has increased profoundly in the last two decades. According to data from the National Health and Nutrition Examination Survey (NHANES), 45% of the US population had serum vitamin D levels of 30 ng/mL (considered adequate for health[2]) in 1998–1994, whereas in 2001–2004, this figure was only 23%, a drop of 49%.[3] Concomitantly, the incidence of erectile dysfunction (ED) is rising: worldwide, the number of men with ED will increase from 150 million in 1995 to an estimated 322 million in 2025.[4] ED is also prevalent in the US, affecting approximately 18–30 million men older than 20 y.[5,6] Much of the worldwide upsurge may be due to an aging population, a deteriorating diet, lack of exercise and other unhealthful practices.

One recent study found risk of ED associated with "body mass index (BMI), irritative lower urinary tract symptoms, diabetes mellitus, chronic obstructive pulmonary disease (COPD) and sexual inactivity."[7]

"Most cases [of ED] have a multifactorial origin and it is admitted the influence on its pathogenesis of systemic diseases, different kind of drugs, psychogenic factors, cardiovascular, endocrinological and neurological diseases. Neurologic causes of erectile dysfunction may have their origins in the central or peripheral nervous system. Among possible process of neurogenic erectile dysfunction of central origin would be tumors, cerebral vascular accidents, encephalitis, Parkinson disease, multiple sclerosis and other demyelinization diseases, dementias, olivopontocerebellar degeneration and epilepsy."[8]

It has been estimated that about half of ED is related to vascular causes.[9] VDD also contributes to ED apart from its negative influence on classic CVD risk factors.

The Role of Vascular Disorders in ED

ED is an inability to produce an erection sufficiently rigid for sexual intercourse. ED incidence increases with age; the most severe form (defined as never being able to achieve an erection) occurs in 2% of men aged 20–39 y, increasing to 47% of men aged 75 y.[10]

The penis is a highly vascularized organ, and erections are primarily vascular events.[11] Sexual stimulation causes the release of neurotransmitters from the corpus cavernosa (the two cylindrical chambers that run the length of the penis) and a relaxing factor, now established as nitric oxide (NO), from the endothelial cells of the penis.[12] NO is particularly important; vasodilation is essential to erection, and NO is the trigger for vasodilation in the vascular endothelium.[13,14] The neurotransmitters, together with NO, cause the corpus cavernosa to relax and allow blood to flow into the penis, causing the penis to expand and sustain an erection until the process is reversed.[15] Any disorder causing endothelial dysfunction (END) will also interfere with vasodilation, which prevents erection. END is an early marker for the development of atherosclerosis.[16] In fact, END is the key factor in the pathophysiology of ED, and men with penile END also have END in other blood vessels.[17]

The increase in the number of patients with CVD risk factors parallels the worldwide increase in ED prevalence,[18] which one would expect given that the two disorders result from intertwined disease processes.[19] Although nonvascular factors such as depression, fatigue, stress, Parkinson disease, multiple sclerosis (MS), and hypertensive medications may affect ED,[12] it is primarily a vasculogenic disease. Its most prevalent cause is the arterial occlusion of atherosclerosis, which also affects the coronary arteries and can lead to heart attack[11] or, in other parts of the body, vascular events such as stroke[20] and peripheral arterial disease (PAD).[21]

Because the penile arteries are smaller than arteries supplying other areas of the body, the first symptoms of atherosclerosis may manifest as ED, making ED one of the best predictors of CVD.[13,22–25] Coronary artery disease is a CVD that is highly predictable by the presence of ED. Jackson and colleagues have stated that after the onset of ED, many men experience CVD symptoms in 2–3 y and then suffer cardiovascular events (such as heart attack or stroke) in 3–5 y.[26] One CVD, PAD, is also associated with the presence of ED. ED is an independent predictor of PAD, and increasing severity of ED is associated with increasing prevalence of PAD.[27]

Bohm and colleagues, after conducting a 2 y, randomized, controlled trial to determine whether ED was a harbinger of CVD events, demonstrated that ED was a potent predictor of myocardial infarction, stroke, and heart failure in men with preexisting CVD. ED also predicted an increased hazard ratio of 1.84 (95% CI, 1.21–2.81; p = 0.005) for all-cause death.[28] In discussing the results of this study and the danger that ED drugs (phosphodiesterase-5 inhibitors) might pose by causing ED patients to ignore the presence of CVD, Bohm observed the following: "The drug works and the patient doesn't show up anymore. These men are being treated for ED, but not the underlying cardiovascular disease. A whole segment of men is being placed at risk."[29] Other researchers have concluded that the presence of ED should trigger an aggressive assessment for occult vascular disease.[11]

Because both CVD and ED are, at least in part, vascular diseases, and ED is a potent predictor of CVD, the presence of risk factors for CVD also predicts the presence of ED,[30] and treatments that improve CVD often also do so for ED. Treatments with lifestyle changes, for example, are quite effective. Gupta and colleagues performed a meta-analysis of randomized, controlled clinical trials and demonstrated that with lifestyle modification and CVD risk-factor reduction programs in men with ED, sexual function increased by 2.4 times with lifestyle changes alone and by 2.66 times when statin therapy was included.[31] One effect of some statins is an increase in serum 25(OH)D concentrations[32]

One effective lifestyle change included a diet rich in whole grains, fruits, vegetables, legumes, walnuts, and olive oil; another was an exercise program (running or vigorous outdoor activity). Optimizing vitamin D levels through sunlight exposure or supplementation was not part of the lifestyle changes, but it should have been: VDD is associated with arterial stiffness and vascular dysfunction.[33,34] Vasculogenic ED results from impaired smooth-muscle relaxation (endothelial-dependent or -independent), occlusion of the cavernosal arteries by atherosclerosis, or both.[17]

The Role of Vitamin D and Sunlight on CVD

VDD is rampant among heart disease patients; University of Kansas researchers found that 70.3% of their heart disease patients had serum vitamin D levels below 30 ng/mL (the measure considered adequate for health) and that supplemental vitamin D was associated with a 61% reduction in the risk of death.[35] Giovannucci and colleagues showed that men with the lowest levels of serum vitamin D had a 2.4-times-increased risk of heart attack.[36]

Possible Influence of Sunlight or Vitamin D on Four Major Risk Factors for CVD and ED

We hypothesize that optimizing vitamin D levels in men with ED could achieve similar positive influences on that disease. We first discuss four classic risk factors for CVD and ED and present research suggesting the influence of sunlight or vitamin D on each factor. We then briefly discuss other influences of vitamin D on ED that have not been thoroughly covered in conjunction with the four common risk factors discussed.

Arterial calcification. Arterial calcification is a common feature of atherosclerosis, occurring in more than 90% of angiographically significant lesions.[37] Measures of arterial calcification have been used since 1964 to predict myocardial infarct,[38] and in 1990, 83–90% of CVD patients showed calcification of their coronary arteries—a far higher percentage than disease-free people.[39] Arterial calcification remains a strong marker of increased risk of CVD,[40,41] independent of other known risk factors.[42,43]

Arterial calcification is also a risk factor for ED. Lee and colleagues demonstrated that men who had ED were about 40% more likely to have measurable coronary artery calcification than those without ED.[44] They concluded that ED "is significantly associated with abnormal coronary artery calcification and, like PAD, might warrant consideration as a coronary artery disease risk equivalent."

Serum vitamin D levels and arterial calcification have a strong inverse relationship,[37] provided that vitamin D levels are not excessively high, which can exacerbate calcification. Zittermann and colleagues explain that vitamin D exerts a biphasic dose–response curve on vascular calcification with deleterious consequences not only for vitamin D excess but also for VDD. They also note, however, that vitamin D excess seldom occurs in the general population.[45] These researchers also mention that in rats, low levels of activated vitamin D (1,25-dihydroxyvitamin D or calcitriol) are associated with massive calcification of blood vessels and other soft tissues.

We hypothesize that optimizing vitamin D levels through sunlight exposure or supplementation would have positive benefits for those suffering from ED associated with vascular calcification.

Diabetes mellitus. Diabetes mellitus (DM) is a disorder of carbohydrate metabolism characterized by excessive glucose levels in urine due either to inadequate production of insulin (insulin-dependent, or type-1 DM) or to poor insulin utilization (adult-onset, or type-2 DM), both of which result in increased urine flow. Ninety percent to 95% of diabetes cases in the US are type-2.[46] The presence of DM is a profound predictor of CVD, correlating to an increased risk of CVD of approximately 2.5 times.[47] Although incidence of CVD has decreased somewhat in the past few decades, it has done so only in those without DM. The incidence of DM rapidly increased from 1970 to 2000,[48] especially during the 1990s, and those with DM have shown a dramatic upsurge in the risk of CVD. For example, during the 1990s, the risk of acute myocardial infarction increased among those with DM by 51%, and general CVD rates in men with DM increased by 61%.[49] Diabetes leads to CVD by causing END, a precursor to atherosclerosis, as follows:[50] High levels of glucose in the blood inhibit the production of NO.[51] This inhibition impairs vasodilation of vessels and leads to atherosclerosis[52] by promoting vasoconstriction, hypertension, vascular smooth-muscle growth, inflammation, expression of cellular adhesion molecules (CAMs), platelet activation, decreased fibrinolysis and thrombosis.[53] Both type-1 and type-2 DM follow this pattern. Awad and colleagues stated that "the diabetes control and complications trial clearly showed that better long-term control of blood glucose in diabetes type-1 is associated with decreased frequency and delayed the onset of microvascular complications."[54] These changes in the vessel walls affect the brain as well as the heart: diabetics younger than 55 y have 11.6 times the risk of stroke.[55]

DM also is associated closely with the risk of ED, as one would expect given how DM damages the vascular system. Reviewing the literature, Phe and Roupret concluded that "the pathophysiology is multifactorial, involving END, specific complications of diabetes and psychological factors."[56] In fact, compared with nondiabetic men, men with DM have three to four times the risk of ED,[57,58] and the likelihood of ED in diabetic men ranges from 35–90%.[59] ED in men with diabetes also occurs 10–15 y earlier.[60]

Sunlight exposure relates to DM. One paper showed that blood sugar levels are lower during summer than in winter,[61] and another showed that exposure to UVB light increases insulin secretion.[62]

Vitamin D research indicates a close association between vitamin D and DM. Pittas and colleagues reported on research conducted on adults with impaired sugar tolerance and insulin resistance (both risk factors for diabetes). For 3 y, half received a placebo and the other half received vitamin D plus calcium. The rise in blood sugar levels was 15 times higher in the placebo group, and their increase in insulin resistance was 18 times higher.[63] Moreover, a 4-week program of high-dose vitamin D supplementation (10,000 IU daily) in subjects with impaired fasting glucose was associated with an improved insulin sensitivity and a decreased acute insulin response to glucose, both risk factors for DM.[64] Finally, a 16-week randomized, placebo-controlled study demonstrated that subjects who took 2,000 IU of vitamin D_3 daily had increased β-cell function, as shown by a 37% improvement in insulin secretion.[65]

We hypothesize that vitamin D optimization through sunlight exposure and/or vitamin D_3 supplementation would decrease END and subsequent vascular damage caused by diabetes and would reduce the risk of ED.

Hypertension and stroke. High blood pressure, or hypertension, especially systolic pressure, is a vascular disorder that is a potent predictor of CVD,[66] and a strong, linear, and independent relationship exists between the two.[67] Hypertension is also one of the most important risk factors for stroke.[68,69] Hypertension leads to END, which is mediated by impaired NO availability after oxidative stress.[16]

Hypertension is also a risk factor for ED,[70] which afflicts to some degree 68% of men with hypertension.[71,72] Because hypertension leads to vascular damage and END, one would expect this outcome. The hypertension–ED–stroke connection is clear in the fact that over a 5-y period, men with ED have a 29% higher risk of stroke than those without ED.[73]

The control of renin and angiotensin also affects hypertension. Renin is an enzyme that profoundly raises blood pressure by activating the peptide angiotensin, a vasoconstrictor.[74] Vitamin D may suppress hypertension by modulating the renin-angiotensin system,[75,76] a regulatory cascade essential in regulating blood pressure.[77] Vitamin D is a potent endocrine suppressor of renin biosynthesis, and VDD stimulates renin expression in normal mice.[75] Also, mice lacking vitamin D receptors produce more renin and angiotensin, leading to hypertension.[77]

A direct relationship exists among hypertension, sunlight exposure, and stroke; the incidence of hypertension is considerably higher in winter than summer. One study of elderly hypertensive subjects showed that blood pressure levels averaged 165/90 in winter but 134/74 in the summer, and both stroke and heart attack rates doubled in winter.[78] Hypertension also follows the same pattern in children.[79] UVB light from sun lamps also effectively treats hypertension. In subjects who participated in three sessions per week of whole-body UVB exposure, vitamin D levels rose 162% after 6 weeks, and blood pressure dropped six points on both systolic and diastolic measurements.[80]

Sunlight exposure's ability to lower blood pressure may also be due to another spectrum of UV light—UVA. Opländer and

colleagues demonstrated that whole-body irradiation with UVA lowered systemic blood pressure by stimulating NO production, significantly increasing intradermal levels of NO. These increased NO levels were accompanied by increased flow-mediated vasodilation of the brachial artery.[81] Such vasodilation could also enhance sexual function in men by lessening ED. Another investigation showed that men with the lowest vitamin D levels also had 6.13 times the risk of developing hypertension; women with the lowest levels had 2.67 times the risk.[82] Other investigations show a close association between VDD and the likelihood of stroke.[83]

We hypothesize that vitamin D optimization through sunlight exposure or vitamin D_3 supplementation would decrease vascular damage caused by hypertension and reduce the risk of ED.

Inflammation in the vascular endothelium. Inflammation is a reaction of damaged tissue that manifests as redness, swelling, pain, tenderness and heat. It is primarily a protective response against injury. Normal vascular endothelium has anti-inflammatory properties, but endothelial function is impaired in the presence of inflammatory conditions and increased oxidative stress.[17,84] When injurious agents persist or healing is disturbed, inflammation, tissue injury and attempts at repair coexist. This combination of factors can lead to chronic inflammation, harming many body systems, including the vascular system.[85] Inflammation drives the formation, progression, and rupture of atherosclerotic plaques; it is one of the stimuli that cause CAMs to further recruit inflammatory blood monocytes that adhere to the endothelium, and through chemotactic stimulus by inflammatory proteins known as chemokines and inflammatory cytokines, enter between the endothelial cells and invade the intima of the blood vessel. In the intima, they mature into macrophages, which engulf lipids and create foam cells, leading to atherosclerotic lesions.[86,87] Macrophages also release growth factors that are destructive to blood vessels.[88-91,] Even subclinical inflammation affects endothelial function and is involved in all stages of atherosclerosis.[17] Thus, the endothelium as well as the entire blood vessel is damaged, and atherosclerosis proceeds.

ED is also closely associated with inflammation. C-reactive protein (CRP), a major marker of inflammation, is significantly higher in patients with ED than in subjects without ED.[92,93] Interestingly, CRP itself reduces production of NO, leading to further vascular damage.[94] Also, CAMs are increased in men with ED who have not manifested cardiovascular risk factors or overt vascular damage.[95] Another marker of inflammation is tumor necrosis factor α (TNFα), an inflammatory cytokine that is markedly elevated in men with ED and is another common link between ED and CVD.[96]

Vitamin D may promote vascular health by inhibiting inflammation.[97] Vitamin D supplements and injections may lower CRP levels as much as 40%[98] and improve cytokine profiles; it inhibits the production of proinflammatory cytokines[99,100] while stimulating the production of anti-inflammatory cytokines.[100,101] One pro-inflammatory cytokine, TNFα, is inversely related to regular exposure to sunlight and artificial sources of UVB among women,[102] and the same is probably true for men. Two CAMs induced by TNFα are also significantly decreased after incubation with activated vitamin D.[103] In addition, Oh and colleagues have shown that in patients with type 2 diabetes, active vitamin D inhibits foam cell formation and suppresses macrophage cholesterol uptake,[104,105] inhibiting the inflammatory atherosclerotic process described earlier.

We hypothesize that vitamin D optimization through sunlight exposure or vitamin D_3 supplementation would decrease vascular damage caused by inflammation and reduce the risk of ED. We searched pubmed.gov for evidence contradicting our hypothesis regarding VDD and ED but found none.

Other influences of vitamin D on ED. *Endothelial-progenitor cells.* Endothelial progenitor cells (EPCs) are necessary for maintaining the health of the arterial endothelium. VDD is associated with depletion of EPCs and consequent END in patients with type 2 DM.[106] This research also showed that VDD was associated with reduced vasodilation as measured by brachial artery flow–mediated dilation.

NO synthases. NO synthases (NOS) are a family of enzymes that catalyze the production of NO from L-arginine. Activated vitamin D stimulates the production of substantial quantities of NOS and NO in macrophages produced in response to tuberculosis,[107] in bone[108] and in endothelial cells,[109] the last being vital to vascular dilation and thereby important to inhibiting ED. This behavior may explain why endothelium-derived, NO-evoked dilation is halved in arteries from vitamin D–deficient male rats.[110]

PAD. PAD is a CVD that is closely associated with the presence of ED. Chua and colleagues have shown that VDD could be an easily correctable independent risk factor for PAD.[111]

Platelet activation. Platelet activation by proinflammatory factors is another aspect of END. In experiments, vitamin D attenuates platelet activation while reducing the expression of two CAMs, VCAM-1 and MT1-MMP.[112] Researchers in Israel also identified 50 patients who had a heart attack or an episode of unstable angina, placing half of them on a regimen of 4,000 IU of vitamin D daily for 5 d. The vitamin D group showed a decrease in VCAM-1 as well as another inflammation marker, interleukin 6. The patients who did not receive vitamin D showed clear increases in both inflammation markers.[113] The researchers stated, "VCAM-1 is central to atherosclerotic plaque formation and [interleukin 6] is broadly associated with coronary risk." Both studies indicate that vitamin D has actions that reduce END and thereby have a positive influence on ED.

Vascular smooth-muscle cell proliferation. Vascular smooth-muscle cell (VSMC) proliferation is part of the process of atherosclerosis. Vitamin D has an antiproliferative influence on VSMC,[114,115] which indicates antiatherosclerotic properties that may positively influence ED.

Vasodilation. Vasodilation is vital to achieving erection. VDD is inversely associated with flow-mediated vasodilation, END, and arterial stiffness irrespective of the traditional risk factors for CVD and ED[33] discussed here. Therefore, VDD—in addition to exacerbating the classical risk factors for CVD—may directly lead to ED.

Nonvascular conditions comorbid with ED and influenced by vitamin D. We have thus far discussed the relationship of ED

to CVD and considered the influence of vitamin D levels or treatment on both disorders. Evidence in addition to that presented in this review in support of the hypothesis that VDD contributes to ED risk was sought by searching pubmed.gov for papers linking ED to sun exposure, race, and disorders linked to VDD, and whether animal models regarding vitamin D and ED had been conducted. No evidence linking ED to sun exposure was found. No animal model studies of ED and vitamin D were found. In a cross-sectional study in the United States in 2000 and 2001, the estimated prevalence of ED was "21.9% (95% CI, 18.8–24.9) in whites, 24.4% (95% CI, 18.4–30.5) in blacks, and 19.9% (95% CI, 13.9–25.9) in Hispanics."[116] Another paper reported that Black and Hispanic men in the Boston area had 25% higher rate of ED, but attributed the finding to socioeconomic status rather than race[117]

Several other nonvascular diseases and conditions are closely associated with both ED and VDD, strengthening the hypothesis that VDD contributes to ED and offering another avenue whereby vitamin D optimization might mitigate or reverse it. Those diseases and conditions include Alzheimer,[118,119] asthma,[120,121] chronic kidney disease,[122-124] depression,[125,126] falls and fractures,[127,128] metabolic syndrome,[129,130] MS,[131-134] obesity,[135,136] Parkinson,[137,138] periodontal disease,[139,140] psoriasis[141,142] and smoking.[143,144] **Table 1** summarizes research regarding those diseases and conditions. For all of these diseases, VDD appears to be an important risk factor. Thus, avoiding VDD earlier in life may reduce the risk of ED. In addition, for some of the diseases such as atopic dermatitis[145,146] and multiple sclerosis, increasing vitamin D intake or production can reduce the symptoms and may also reduce the risk of ED.

Conclusion

The research presented suggests that many common mechanisms underlie both CVD and ED, and that VDD is closely associated with both disorders. We hypothesize that optimizing serum vitamin D levels through sunlight exposure or vitamin D supplementation helps delay the onset of ED. Coupled with positive changes in lifestyle, such optimization may restore normal sexual function to some men. This hypothesis should be tested through observational and intervention studies. If proven by further research, such therapy would offer an alternative or complement to phosphodiesterase-5 inhibitors, which, though exceptionally effective and a first choice for treatment, have been associated with many negative side effects,[147] and which, because of their efficacy in producing erections, may cause men with ED to ignore the possibility they might have occult underlying CVD.

Table 1. Evidence for influences of vitamin D on nonvascular diseases and conditions associated with ED

Disease or condition	Finding (some measure of correlation)	Reference	Evidence for vitamin D deficiency
Alzheimer disease	Loss of erection was reported in 53% of 55 male Alzheimer disease patients with a mean age of 70.25 y. Loss of erection is not related to degree of cognitive impairment, age, or depression.	118	119
Asthma	Subjects with asthma experienced a 1.9-fold (95% CI, 1.3–2.9; p = 0.002) increase in incident ED.	120	121
Chronic kidney disease	Prevalence of ED of various degrees was 87.7% among 73 patients with chronic kidney disease in Iran.	122	123,124
Depression	Comorbid conditions ED and depression are highly prevalent in men, and men with high depression scores are nearly twice as likely to report ED than nondepressed men.	125	126
Falls, fractures	ED (2.01; 95% CI, 1.30–3.09) was associated with increased risk of osteoporotic fractures in adjusted models.	127	128
Metabolic syndrome	Metabolic syndrome appears to be strongly related to ED.	129	130
Multiple sclerosis	91% of men with multiple sclerosis report having symptoms of either ED or impotence.	131,132	133,134
Obesity	Obesity in Taiwanese military conscripts predicted more than an 83-times-increased risk of ED.	135	136
Parkinson disease	ED was severe in 54% of Parkinson cases and moderate in 26.6%.	137	138
Periodontal disease	Chronic periodontal disease was significantly more prevalent among men with mild ED (p = 0.004) and moderate to severe ED (p = 0.007) than in men without ED.	139	140
Psoriasis	Patients with ED were more likely to have been diagnosed with psoriasis before the index date than controls (odds ratio = 3.85; 95% CI l = 2.72–5.44)	141	142
Smoking	In comparison with never smokers, the OR of ED was 2.41 for current smokers and 2.15 for ex-smokers and increased with duration of the habit.	143	144
Atopic dermatitis	cases were more likely to have prior AD than controls (OR = 1.60; 95% CI = 1.42–1.80, p < 0.001) after multifactorial adjustment	145	146

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