ORIGINAL CONTRIBUTION

Serum Vitamin D and the Risk of Parkinson Disease

Paul Knekt, DPH; Annamari Kilkkinen, PhD; Harri Rissanen, MSc; Jukka Marniemi, PhD; Katri Sääksjärvi, MSc; Markku Heliövaara, PhD

Objective: To investigate whether serum vitamin D level predicts the risk of Parkinson disease.

Design: Cohort study.

Setting: The study was based on the Mini-Finland Health Survey, which was conducted from 1978 to 1980, with Parkinson disease occurrence follow-up through the end of 2007. During the 29-year follow-up period, 50 incident Parkinson disease cases occurred. Serum 25-hydroxyvitamin D level was determined from frozen samples stored at baseline. Estimates of the relationship between serum vitamin D concentration and Parkinson disease incidence were calculated using the Cox model.

Participants: Three thousand one hundred seventy-three men and women, aged 50 to 79 years and free of Parkinson disease at baseline.

Main Outcome Measure: Parkinson disease incidence.

Results: Individuals with higher serum vitamin D concentrations showed a reduced risk of Parkinson disease. The relative risk between the highest and lowest quartiles was 0.33 (95% confidence interval, 0.14-0.80) after adjustment for sex, age, marital status, education, alcohol consumption, leisure-time physical activity, smoking, body mass index, and month of blood draw.

Conclusions: The results are consistent with the suggestion that high vitamin D status provides protection against Parkinson disease. It cannot, however, be excluded that the finding is due to residual confounding and further studies are thus needed.

Arch Neurol. 2010;67(7):808-811.

Author Affiliations: National Institute for Health and Welfare, Helsinki, Finland.

VITAMIN D PLAYS AN IMPORTANT role in the pathogenesis of skeletal disorders and calcium homeostasis.[1] Vitamin D inadequacy also predicts increased risk of other chronic conditions, eg, cancer,[2] cardiovascular diseases,[3] and type 2 diabetes mellitus.[4] Recently, chronically inadequate vitamin D intake was proposed to play a significant role in the pathogenesis of Parkinson disease.[5] According to the suggested biological mechanism, Parkinson disease may be caused by a continuously inadequate vitamin D status leading to a chronic loss of dopaminergic neurons in the brain. The epidemiological evidence of an association between vitamin D and Parkinson disease is, however, limited to cross-sectional studies[6-8] showing lower vitamin D status in patients with Parkinson disease compared with healthy controls.

Parkinson disease is a major cause of disability in elderly individuals. Its risk factors are relatively unknown. However, both biological plausibility and epidemiological data indicate that vitamin D deficiency may contribute to its development.[5] The present cohort study investigated whether serum 25-hydroxyvitamin D level predicts Parkinson disease incidence in a population from northern latitudes where exposure to the sun is limited and therefore vitamin D status is continuously low.

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METHODS

The Mini-Finland Health Survey, carried out from 1978 to 1980 in 40 areas of Finland, was based on a 2-stage cluster sample (n=3637 men and n=4363 women) drawn from the population register to represent Finnish adults 30 years and older.[9] A total of 7217 individuals (90% of the sample) participated in the survey. Of these, 3173 individuals, aged 50 to 79 years, free of Parkinson disease and not using antipsychotic medication to treat psy-

chotic disorders (*International Statistical Classification of Diseases, 10th Revision* codes F20-F39), were included in the present study.

Information on socioeconomic background, diseases, medications, and lifestyle was collected via questionnaires and interviews.[9] At the baseline examinations, height and weight were measured, and the body mass index was calculated as weight in kilograms divided by height in meters squared. Casual blood pressure was measured with the auscultatory method and hypertension was defined as systolic blood pressure 160 mm Hg or higher and diastolic blood pressure 95 mm Hg or higher or the use of antihypertensive medication. Blood samples were taken and the cholesterol concentrations determined by an autoanalyzer modification (Auto-Analyzer Methodology N-24a and N-77; Technicon, Tarrytown, New York) of the Liebermann-Burchard reaction. The serum samples were kept frozen at –20°C until 2002, when serum 25-hydroxyvitamin D concentrations were determined using radioimmunoassay (DiaSorin, Stillwater, Minnesota). The interassay coefficient of variation of 25-hydroxyvitamin D concentration determination was 7.8% at the mean level of 47.3 nmol/L (n=167). The intra-assay coefficient of variation was 6.4%. The samples were run as single samples. The right assay level was ensured by using the reference serum validated by the National Institute of Standards and Technology (Standard Reference Material 968c Fat-Soluble Vitamins; National Institute of Standards and Technology, Gaithersburg, Maryland). The laboratory also participates in the external quality control program run by Labquality Oy (Helsinki, Finland). In addition, the laboratory's vitamin D concentration measurement method is accredited by the Finnish Accreditation Service (FINAS, T077).

Parkinson disease cases (*International Statistical Classification of Diseases, 10th Revision* code G20) were identified through linkage with the nationwide Drug Imbursement Register of the Social Insurance Institution, using individual social security codes as the identity link. All individuals in Finland with Parkinson disease are eligible for medication free of charge. To obtain this allowance, the patient must apply for it and attach a certificate written by the treating neurologist stating that all the diagnostic criteria for Parkinson disease are met. This certificate must include symptom history and reports of clinical findings, including the presence of resting tremor, bradykinesia, and/or muscle rigidity. A Social Insurance Institution neurologist must agree with the diagnosis as described on the certificate for medication costs to be reimbursed. In an ongoing validation of the register, the certificates for Parkinson disease drug reimbursement and selected hospital records were reevaluated retrospectively by a neurologist according to the National Institute of Neurological Disorders and Stroke diagnostic criteria for Parkinson disease.[10,11] Of the originally identified Parkinson disease cases reviewed, 80% met criteria for Parkinson disease (J. Lyytinen, MD, PhD, oral communication, January 2009), consistent with other estimates of the percentage of people clinically diagnosed with parkinsonism in a general population who meet strict Parkinson disease criteria.[12] The follow-up time was defined as the number of days from the baseline examination to the dates of Parkinson disease occurrence, death, or end of follow-up, whichever came first. During a 29-year follow-up from 1978 to 2007, 50 Parkinson disease cases were identified.

The Cox proportional hazards model was used to estimate the strength of association between serum vitamin D level and Parkinson disease incidence as relative risks (RRs) and their 95% confidence intervals (CIs) between quartiles of serum vitamin D level.[13] Test for trend was based on the likelihood ratio test by including serum vitamin D level as a continuous variable in the 3 models. The first model included age and sex as potential confounders. The second model further included marital status, education, alcohol consumption, leisure-time physical activity, smoking status, body mass index, and month of blood draw. In a third model, the eventual intermediary variables hypertension and total serum cholesterol level were further included. Potential effect modification of sex, age, season, hypertension, body mass index, and serum cholesterol level on the association between vitamin D level and Parkinson disease incidence was studied by including interaction terms in the second model. All analyses were carried out using SAS software version 9 (SAS Institute Inc, Cary, North Carolina).

Table 1. Selected Sex- and Age-Adjusted Baseline Characteristics by Parkinson Disease

	Parkinson Disease, %		
	Noncases (n = 3123)	Cases (n = 50)	*P* for Heterogeneity
Age,[a] y, mean (SD)	61.8 (8.0)	60.4 (6.5)	.23
Male[b]	43.1	47.2	.56
Summer season, Jun-Sep	18.3	12.7	.25
More than basic education	19.8	23.2	.55
Married	65.9	68.7	.66
Regular leisure-time physical activity	11.3	7.6	.42
Smoker	18.7	6.2	.02
Alcohol consumption, grams of ethanol/wk, mean (SD)	29.6 (86.2)	13.1 (51.1)	.15
Hypertension	35.7	21.1	.03
Body mass index,[c] mean (SD)	26.8 (4.2)	26.5 (3.3)	.62
Diabetes mellitus	8.7	2.7	.13
Serum total cholesterol level, mg/dL, mean (SD)	283.4 (52.9)	279.9 (51.7)	.65
Serum 25-hydroxyvitamin D level, nmol/L, mean (SD)	41.8 (19.5)	36.3 (18.5)	.05

SI conversion factor: To convert total cholesterol to millimoles per liter, multiply by 0.0259.
[a] Adjusted for sex.
[b] Adjusted for age.
[c] Calculated as weight in kilograms divided by height in meters squared.

RESULTS

At baseline, Parkinson disease cases more often were nonsmokers and did not have hypertension or diabetes than subjects who were free of the disease (**Table 1**). Serum vitamin D concentration was lower among Parkinson disease cases and it was also associated with age, sex, marital status, education, leisure-time physical activity, smoking, alcohol consumption, body mass index, diabetes, hypertension, serum cholesterol level, and the season of measurement (**Table 2**).

A significant inverse association between sex- and age-adjusted serum vitamin D level and Parkinson disease incidence was found (**Table 3**). The RR of the disease between the highest and lowest quartiles of vitamin D concentration was 0.35 (95% CI, 0.15-0.81; *P* for trend=.006). After further adjustment for the potential

Table 2. Selected Sex- and Age-Adjusted Baseline Characteristics by Serum 25-Hydroxyvitamin D Level Quartiles[a]

	Serum 25-Hydroxyvitamin D Level, %				
	Quartile 1 (n = 774)	Quartile 2 (n = 819)	Quartile 3 (n = 778)	Quartile 4 (n = 792)	*P* for Trend
Age,[b] y, mean (SD)	63.8 (8.1)	62.2 (8.1)	61.2 (7.8)	60.0 (7.6)	<.001
Male[c]	45.1	43.4	42.6	41.8	.18
Summer season, Jun-Sep	2.7	12.7	21.1	36.1	<.001
More than basic education	12.7	18.3	24.6	23.7	<.001
Married	61.9	65.6	65.8	70.5	<.001
Regular leisure-time physical activity	5.5	10.3	12.9	15.9	<.001
Smoker	22.3	17.3	18.8	15.6	.002
Alcohol consumption, grams of ethanol/wk, mean (SD)	22.0 (71.3)	25.9 (72.1)	32.0 (96.1)	37.6 (98.8)	<.001
Hypertension	37.2	36.6	35.5	32.4	.04
Body mass index,[d] mean (SD)	26.7 (4.6)	27.1 (4.3)	27.1 (4.0)	26.2 (3.6)	.03
Diabetes mellitus	11.2	8.9	8.2	6.1	<.001
Serum total cholesterol level, mg/dL, mean (SD)	277.6 (54.4)	281.9 (52.1)	285.3 (52.9)	288.8 (51.0)	<.001

SI conversion factor: To convert total cholesterol to millimoles per liter, multiply by 0.0259.
[a] Quartiles for men: 8 to 28, 29 to 41, 42 to 56, and 57 to 159 nmol/L; for women: 7 to 25, 26 to 36, 37 to 49, and 50 to 151 nmol/L.
[b] Adjusted for sex.
[c] Adjusted for age.
[d] Calculated as weight in kilograms divided by height in meters squared.

Table 3. RRs With 95% CIs for Parkinson Disease Cases by Baseline Serum 25-Hydroxyvitamin D Level[a]

	Serum 25-Hydroxyvitamin D Level, RR (95% CI)				
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*P* for Trend
No. of Parkinson disease cases	17	15	10	8	
Sex- and age-adjusted model	1[Reference]	0.73 (0.36-1.46)	0.47 (0.21-1.03)	0.35 (0.15-0.81)	.006
Multivariate model A[b]	1[Reference]	0.72 (0.36-1.46)	0.48 (0.22-1.08)	0.33 (0.14-0.80)	.006
Multivariate model B[c]	1[Reference]	0.72 (0.36-1.45)	0.48 (0.21-1.07)	0.33 (0.14-0.78)	.005

Abbreviations: CI, confidence interval; RR, relative risk.
[a] Quartiles for men: 8 to 28, 29 to 41, 42 to 56, and 57 to 159 nmol/L; for women: 7 to 25, 26 to 36, 37 to 49, and 50 to 151 nmol/L.
[b] Model A further included marital status (married or other), education (basic or intermediate/high), alcohol consumption (0, <5, or ≥5 g/d), leisure-time physical activity (no/light or heavy), smoking status (none or current), body mass index, and month of blood draw.
[c] Model B further included hypertension and serum cholesterol level.

confounders, including body mass index, leisure-time physical activity, smoking, education, marital status, alcohol consumption, and month of blood draw, the association persisted (RR, 0.33; 95% CI, 0.14-0.80; *P* for trend = .006). Further adjustment for serum cholesterol level and hypertension or exclusion of the disease cases occurring during the first 2 years of follow-up did not notably alter the results either. Inclusion of an interaction term between vitamin D level and sex, age, body mass index, serum cholesterol level, blood pressure, and the season of measurement did not notably alter the results (data not shown).

COMMENT

This cohort study shows that low serum vitamin D level predicts an elevated risk of Parkinson disease incidence. Individuals with a serum vitamin D concentration of at least 50 nmol/L had a 65% lower risk than those with values less than 25 nmol/L after adjustment for several potential confounders. Despite the overall low vitamin D levels in the study population, a dose-response relationship was also found.

Vitamin D is obtained from diet and is photosynthesized in the skin by the action of solar UV-B radiation. This study was carried out in Finland, an area with restricted sunlight exposure, and is thus based on a population with a continuously low vitamin D status. Accordingly, the mean serum vitamin D level in the present population was about 50% of the suggested optimal level (75-80 nmol/L).[14] Our findings are thus consistent with the hypothesis[5] that chronic inadequacy of vitamin D is a risk factor for Parkinson disease.

As far as we know, this is the first longitudinal study to investigate the association between vitamin D status and subsequent Parkinson disease occurrence. In line with our finding, however, previous cross-sectional studies demonstrated the higher prevalence of hypovitaminosis D in patients with Parkinson disease than in healthy controls.[6-8] The exact mechanisms by which vitamin D may protect against Parkinson disease are not fully understood. Vitamin D has, however, been shown to exhibit neuroprotective effects through antioxidative mechanisms, neuronal calcium regulation, immunomodulation, enhanced nerve conduction, and detoxification mechanisms.[5,15,16]

The vitamin D receptors and an enzyme responsible for the formation of the active form 1,25-hydroxyvitamin D have been found in high levels in the substantia nigra, the region of the brain affected most by Parkinson disease.[15] This raises the possibility that chronic inadequacy of vitamin D leads to the loss of dopaminergic neurons in the substantia nigra region and further Parkinson disease.

The strengths of the present study are the apparent long-term inadequacy of vitamin D[17] and the prospective design. There are, however, some weaknesses. First, the small number of cases may have caused instable results. Second, only a single measurement of serum 25-hydroxyvitamin D was available, which fails to take into account the intraindividual seasonal variation. However, no measurements were carried out during July and no interaction between serum vitamin D concentration and season (sunny vs dark period) was observed. Serum vitamin D level is relatively stable over time.[18] The possibility that levels changed during long-term storage cannot, however, be excluded.[19,20] Third, it is possible that the study population includes undefined Parkinson disease cases and also that all patients with Parkinson disease diagnoses are not definite cases. Because of the low prevalence of the disease, the former error is not of great importance. The latter error may, however, have biased the estimates of the strength of association. Fourth, the limited information on dietary intake of vitamin D is of potential concern. The major dietary source of vitamin D is fatty fish, whose consumption is also suggested to be beneficial against Parkinson disease because of ω-3 polyunsaturated fatty acids.[21] The findings are, however, contradictory,[22] and vitamin D level has several other determinants.[23] Fifth, the risk factors for Parkinson disease are not well known, and therefore, despite comprehensive adjustments for potential confounders, residual confounding may still remain.

In conclusion, our results are in line with the hypothesis that low vitamin D status predicts the development of Parkinson disease. Because of the small number of cases and the possibility of residual confounding, large cohort studies are needed. In intervention trials focusing on effects of vitamin D supplements, the incidence of Parkinson disease merits follow up.

Accepted for Publication: September 8, 2009.
Correspondence: Paul Knekt, DPH, National Institute for Health and Welfare, PL 30, 00271 Helsinki, Finland (paul.knekt@thl.fi).
Author Contributions: Prof Knekt had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Knekt and Kilkkinen. *Acquisition of data:* Knekt, Marniemi, and Heliövaara. *Analysis and interpretation of data:* Knekt, Kilkkinen, Rissanen, and Sääksjärvi. *Drafting of the manuscript:* Knekt. *Critical revision of the manuscript for important intellectual content:* Knekt, Kilkkinen, Rissanen, Marniemi, Sääksjärvi, and Heliövaara. *Statistical analysis:* Knekt. *Obtained funding:* Knekt. *Administrative, technical, and material support:* Kilkkinen. *Study supervision:* Knekt.

Financial Disclosure: None reported.
Funding/Support: This work was supported by National Institutes of Health grant NIH/NIEHS R01 ES012667.
Role of the Sponsor: The National Institutes of Health did not participate in the design or conduct of the study; the collection, analysis, or interpretation of the data; or the preparation, review, or approval of the manuscript.

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