

Dairy foods intake and risk of Parkinson's disease: a dose–response meta-analysis of prospective cohort studies

Wenjie Jiang · Chuanxia Ju · Hong Jiang · Dongfeng Zhang

Received: 9 December 2013 / Accepted: 22 May 2014
© Springer Science+Business Media Dordrecht 2014

Abstract Dairy foods have been linked to Parkinson's disease (PD), and a meta-analysis of prospective cohort studies on dairy foods intake and PD risk was conducted. Eligible studies were identified in a literature search of EMBASE and PubMed up to April 2014. Seven results from prospective studies were included, including 1,083 PD cases among 304,193 subjects. The combined risk of PD for highest vs. lowest level of dairy foods intake was 1.40 (1.20–1.63) overall, 1.66 (1.29–2.14) for men and 1.15 (0.85–1.56) for women. For highest vs. lowest level, the PD risk was 1.45 (1.23–1.73) for milk, 1.26 (0.99–1.60) for cheese, 0.95 (0.76–1.20) for yogurt and 0.76 (0.51–1.13) for butter. The linear dose–response relationship showed that PD risk increased by 17 % [1.17 (1.06–1.30)] for every 200 g/day increment in milk intake ($P_{\text{for non-linearity}} = 0.22$), and 13 % [1.13 (0.91–1.40)] for every 10 g/day increment in cheese intake ($P_{\text{for non-linearity}} = 0.39$). The absolute risk differences were estimated to be 2–4 PD cases

per 100,000 person-years for every 200 g/day increment in milk intake, and 1–3 PD cases per 100,000 person-years for every 10 g/day increment in cheese intake. Dairy foods (milk, cheese) might be positively associated with increased risk of PD, especially for men.

Keywords Dairy foods · Parkinson's disease · Meta-analysis

Introduction

Parkinson's disease (PD), the second most common neurodegenerative disorder, has a complex etiology and pathophysiology generated by combined effects of genes and environment factors [1]. However, the known PD genes were estimated to account for only a small proportion of all PD [1]. Because of the relatively low incidence of PD and its insidious onset, relatively small number of lifestyle-related factors have been identified, and the most consistent associations were those between smoking and coffee drinking and reduced PD risk [1, 2], and exposure to pesticides and increased PD risk [1, 3]. Dairy foods were hypothesized to increase PD risk by contributing to exposure to pesticides and other neurotoxins, and reducing serum uric acid concentrations [4, 5] that is inversely associated with PD risk and could delay the PD progression [6]. While long-term randomized trials are difficult to implement on a practical basis, several observational studies were conducted to examine the association of dairy foods with PD risk, and the magnitude of association varies among studies [7–10]. Given studies with relatively small number of participants might be underpowered to detect the effect, and even small health effects of dairy foods on risk of PD could have considerable public health

Electronic supplementary material The online version of this article (doi:10.1007/s10654-014-9921-4) contains supplementary material, which is available to authorized users.

W. Jiang (✉) · D. Zhang
Department of Epidemiology and Health Statistics, Qingdao University Medical College, Dongzhou Road, No.38, Qingdao 266021, Shandong, People's Republic of China
e-mail: jiangwjgd@aliyun.com

C. Ju
Department of Pharmacology, Qingdao University Medical College, Qingdao 266021, People's Republic of China

H. Jiang
Department of Physiology, Shandong Provincial Key Laboratory of Pathogenesis and Prevention of Neurological Disorders and State Key Disciplines Physiology, Qingdao University Medical College, Qingdao, People's Republic of China

consequences considering the popularity of dairy foods, we conducted a meta-analysis of prospective cohort studies to assess the association of dairy foods with PD risk.

Materials and methods

A literature search was performed using the databases of PubMed and EMBASE up to April 2014 by two investigators, using the following search terms: dairy or milk and Parkinson's disease without restrictions. Reference lists from retrieved articles were also reviewed. Prospective cohort studies (dairy foods intake was ascertained before the onset of PD) were included if a risk estimate [e.g., hazard ratio, relative risk (RR) or incidence rate ratios] with its (95 % CI) of PD associated with dairy intake was available, and the pooled risk estimate was presented as RR. For dose–response analysis, the number of cases and participants or person-years for each category of dairy intake must be provided. We extracted RR (95 % CI) that reflected the greatest degree of control for potential confounders. The results of different types of dairy foods were first combined within the study if the effect for total dairy was not provided [7]. Results for men and women were included as separate results if the overall result was not provided. We used 240 g as a serving size for milk and 52 g as a serving size for cheese [9] in one study reporting dairy foods intakes by servings [11], and we used 28.35 g as 1 oz in one study [10].

I² was used to assess heterogeneity. Study-specific result was combined using random effect model. Sensitivity analysis was performed with one study removed at a time to assess whether the results could have been affected markedly by a single study. Publication bias was evaluated using Egger test. To examine a potential nonlinear relationship, the two-stage random-effects dose–response meta-analysis [12] was used. Briefly, we first created restricted cubic splines (3 knots at 25, 50 and 75 percentiles) and then we assessed departure from a linear trend by testing the coefficient of the second spline equal to zero. We calculated the absolute risk differences associated with milk intake by multiplying the background incidence rate of PD with (estimated RR – 1). STATA version 12.0 (Stata Corporation, College Station, TX, USA) was used, with probabilities (*P* values) ≤ 0.05 considered statistically significant.

Results

The detailed literature search for articles inclusion was shown in supplementary Fig. 1. Seven results from five prospective cohort studies [7–11] were included, including

1,083 PD cases among 304,193 subjects. Three studies were conducted in USA, one in Finland and one in Greece. The maximum follow-up duration ranged from 8.45 to 41 years. Four case–control studies were excluded because of a retrospective design. The detailed information of the studies is shown in Table 1.

The pooled RR (95 % CI) of PD risk for highest vs. lowest level of dairy food intake was 1.40 (1.20–1.63, I² = 8.20 %) overall, 1.66 (1.29–2.14, I² = 0.00 %) for men and 1.15 (0.85–1.56, I² = 0.00 %) for women (Fig. 1). The combined result was 1.29 (1.07–1.56, I² = 0.00 %) for studies conducted in Europe and 1.56 (1.19–2.05, I² = 27.4 %) for studies conducted in USA. Milk [1.45 (1.23–1.73), I² = 16.1 %], but not cheese [1.26 (0.99–1.60), I² = 29.2 %], yogurt [0.95 (0.76–1.20), I² = 14.6 %] and butter [0.76 (0.51–1.13), I² = 0.00 %] was found significantly associated with PD risk (supplementary Fig. 2).

Sensitivity analysis showed that no individual study had excessive influence on the pooled effect (supplementary Fig. 3). No evidence of publication bias was found overall (*P* = 0.62, supplementary Fig. 4).

Only milk and cheese intake was included in the dose–response analysis because of limited data for total dairy foods and others. For milk, data from four articles [7, 9–11] including 785 PD cases was used, and departure from linear relationship was not significant (*P*_{for non-linearity} = 0.22). The risk of PD was 1.15 (1.03–1.28), 1.29 (1.07–1.57), 1.42 (1.12–1.81), 1.48 (1.18–1.90), 1.53 (1.21–1.93), 1.58 (1.20–2.03), 1.61 (1.16–2.24) for 100, 200, 300, 400, 500, 600 and 700 g/day of milk intake (Fig. 2), respectively. The risk of PD increased by 17 % [1.17 (1.06–1.30)] for every 200 g/day increment in milk intake. The absolute risk difference associated with every 200 g/day increment in milk intake, based on the background incidence rate of PD in the general European population (between 9 and 22 per 100,000 person-years) [1], was estimated to be 2–4 PD cases per 100,000 person-years.

For cheese, data from 3 articles [7, 9, 11] including 659 PD cases was used. The departure from linear relationship was not significant (*P*_{for non-linearity} = 0.39), and the risk of PD increased by 13 % [1.13 (0.91–1.40)] for every 10 g/day increment in cheese intake (supplementary Fig. 5). The absolute risk difference associated with every 10 g/day increment in cheese intake was estimated to be 1–3 PD cases per 100,000 person-years.

Discussion

In this meta-analysis, dairy foods intake was found significantly associated with increased risk of PD overall and

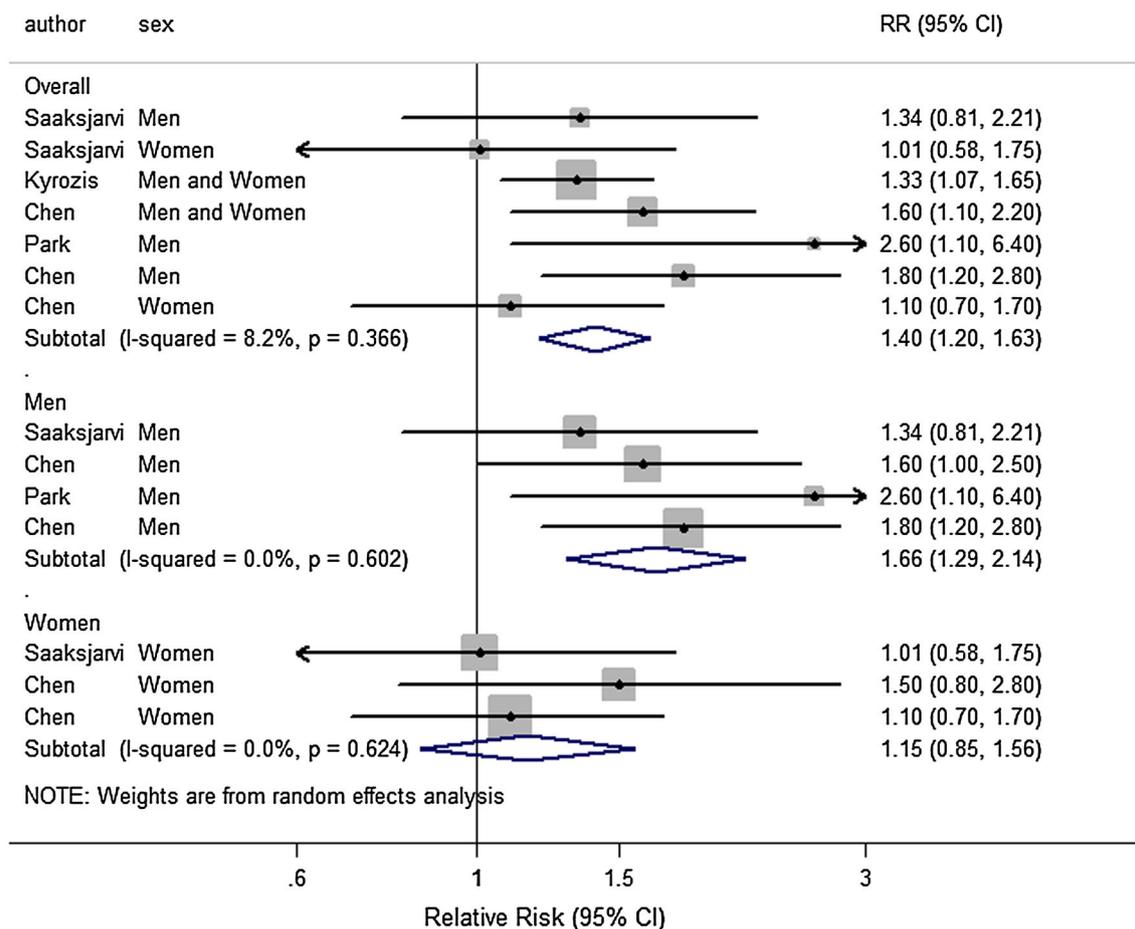


Fig. 1 The forest plot for dairy intake (highest vs. lowest category) and risk of Parkinson's disease. The size of gray box is positively proportional to the weight assigned to each study, which is inversely proportional to the standard error of the RR, and horizontal lines

represent the 95 % confidence intervals. The results of margarine, butter and total milk and milk product were combined as the result for total dairy foods with a random effect model in the study by Sääksjärvi et al. [7]

in men, and milk and cheese might contribute to the observed association. The linear dose-response relationship showed that risk of PD increased by 17 % [1.17 (1.06–1.30)] for every 200 g/day increment in milk intake, and 13 % [1.13 (0.91–1.40)] for every 10 g/day increment in cheese intake.

Statistically significant protective effects of serum urate on PD risk was observed in men [0.60 (0.40–0.90)] but not in women. A dose-response trend of serum urate to reduce PD risk was also observed [0.77 (0.68–0.88)] [6], and dairy foods were also found inversely associated with serum urate concentrations [4, 5]. In addition to pesticides and other neurotoxins contaminating dairy foods, higher dairy calcium, dairy vitamin D intake and dairy protein were also found to significantly (or marginally) increase PD risk in prospective cohort studies [9, 11], and subjects having calcium intake of ≥ 316 mg/day reported a higher age-adjusted incidence of PD than that of < 316 mg/day ($P = 0.046$) [10]. However, dairy fat was found not associated with PD risk [9], and similar results were found

between total dairy foods and low-fat dairy foods, and whole milk and low-fat milk [11].

Certain subtle clinical manifestations may precede diagnosis by up to several years, however, reverse causation should be excluded because similar or ever stronger association was found after excluding individuals who had developed PD during the first 2 [9], 5 [7] and 6 [11] years of the follow-up. All of five studies adjusted for smoking, and no significant differences were found in analyses stratified by baseline smoking status (never smoker or ever smoker) [9, 11]. Significant associations were found in the three studies adjusting for coffee/caffeine [8, 10, 11] and significant association was also found after adjusting for pesticide use [9].

The dose-response analysis showed that the PD risk increased with increasing intake of milk and cheese, respectively. Dose-response analysis was not conducted for total dairy foods [9], yogurt [9, 11] and butter [7, 11] because of limited data. In the included studies, statistical significance of a linear trend was also found by including

Table 1 Characteristics of prospective cohort studies on dairy foods intake and risk of Parkinson's disease (PD) included in this meta-analysis

| Author | Study, country | Subjects (incident PD cases) | Sex | Maximum of follow-up years | Exposure | RR (95% CI) for the highest versus lowest categories | Covariates adjusted | | | | | | |
|------------------------------------|---------------------------------------|------------------------------|------|----------------------------|-------------------------|--|--|--------------|---|------|-------------|----------------------------|---|
| Saaksjarvi et al. [7] ^a | Finnish Mobile Clinic Survey, Finland | 4524 (85) | 41 | M | Margarine | >4 versus ≤1 g/day | Age, sex, marital status, community density, geographical area, smoking, body mass index, leisure-time physical activity, energy, hypertension, serum total cholesterol, diabetes and, in addition, in women, parity | | | | | | |
| | | | | | | 1.78 (0.76–4.16) | | | | | | | |
| | | | | | | 1.25 (0.53–2.97) | | | | | | | |
| | | | | | | >60 versus ≤38 g/day | | | | | | | |
| | | | | | | 1.04 (0.43–2.49) | | | | | | | |
| | | | | | | 0.70 (0.26–1.84) | | | | | | | |
| | | | | | | >1142 versus ≤764 g/day | | | | | | | |
| | | | | | | 1.26 (0.52–3.06) | | | | | | | |
| | | | | | | 1.13 (0.40–3.21) | | | | | | | |
| | | | | | | >950 versus ≤545 g/day | | | | | | | |
| | | | | | | 1.24 (0.48–3.17) | | | | | | | |
| | | | | | | 3.31 (1.10–9.93) | | | | | | | |
| Kyrozis et al. [8] | EPIC–Greece cohort, Greece | 25407 (88) | 8.45 | Both | Fermented milk products | >150 versus <1 g/day | Age, sex, marital status, education, farming, smoking, coffee with caffeine, body mass index, physical activity and energy intake | | | | | | |
| | | | | | | 1.71 (0.79–3.70) | | | | | | | |
| | | | | | | 0.76 (0.32–1.80) | | | | | | | |
| | | | | | | >10 versus ≤2 g/day | | | | | | | |
| | | | | | | 0.83 (0.39–1.80) | | | | | | | |
| | | | | | | 0.84 (0.35–2.00) | | | | | | | |
| | | | | | | 1 SD | | | | | | | |
| | | | | | | Chen et al. [9] | CPS II NC, USA | 130864 (388) | 9 | Both | Total dairy | >502.0 versus ≤133.6 g/day | Age, sex, smoking, energy intake, ibuprofen use, vigorous physical activity, educational level, and pesticide use |
| | | | | | | | | | | | | 1.33 (1.07–1.65) | |
| | | | | | | | | | | | | 1.34 (1.14–1.58) | |
| | | | | | | | | | | | | 0.86 (0.65–1.15) | |
| | | | | | | | | | | | | 1.14 (0.84–1.56) | |
| 1.6 (1.1–2.2) | | | | | | | | | | | | | |
| >397.1 versus ≤84.3 g/day | | | | | | | | | | | | | |
| 1.7 (1.2–2.4) | | | | | | | | | | | | | |
| >19.6 versus ≤1.7 g/day | | | | | | | | | | | | | |
| 1.3 (0.9–1.8) | | | | | | | | | | | | | |
| >92.9 versus 0 g/day | | | | | | | | | | | | | |
| 0.9 (0.6–1.3) | | | | | | | | | | | | | |
| >35 versus 0 g/day | | | | | | | | | | | | | |
| 1.1 (0.8–1.5) | | | | | | | | | | | | | |

Table 1 continued

| Author | Study, country | Subjects (incident PD cases) | Sex | Maximum of follow-up years | Exposure | RR (95 % CI) for the highest versus lowest categories | Covariates adjusted |
|----------------------------|-----------------------------|------------------------------|-----|----------------------------|-------------|---|--|
| Park et al. [10] | Honolulu Heart Program, USA | 7504 (128) | M | 30 | Milk | >16 versus 0 oz/day | Age, coffee intake, pack-years of smoking, physical activity, tricep skinfold thickness, total kilocalories and fat intake, and years worked on a plantation |
| Chen et al. [11] | HPFS NHS, USA | 47331 (210) 88563 (184) | M | 12 | Total dairy | 2.6 (1.1–6.4) | Age, lengths of follow-up, smoking, energy intake, caffeine intake, body mass index, alcohol consumption, and physical activity |
| | | | | | | >2.9 versus < 1 servings/day | |
| | | | | | | 1.8 (1.2–2.8) | |
| | | | | | | 1.1 (0.7–1.7) | |
| | | | | | | ≥ 1 versus 0 servings/day | |
| | | | | | | 1.1 (0.6–1.9) | |
| | | | | | | ≥ 1 versus 0 servings/day | |
| | | | | | | 1.4 (0.9–2.0) | |
| | | | | | | > 1 versus 0 serving/week | |
| | | | | | | 1.9 (1.1–3.1) | |
| ≥ 5 versus 0 servings/week | | | | | | | |
| 1.7 (0.9–3.0) | | | | | | | |
| > 1 versus 0 serving/week | | | | | | | |
| 1.7 (1.0–2.9) | | | | | | | |
| > 1 versus 0 serving/week | | | | | | | |
| 0.9 (0.6–1.4) | | | | | | | |
| > 1 versus 0 serving/week | | | | | | | |
| 0.8 (0.6–1.2) | | | | | | | |
| > 1 versus 0 serving/week | | | | | | | |
| 1.3 (0.8–2.0) | | | | | | | |
| > 1 versus 0 serving/week | | | | | | | |
| 1.3 (0.8–2.2) | | | | | | | |
| ≥ 1 versus 0 serving/day | | | | | | | |
| 0.8 (0.4–1.7) | | | | | | | |
| ≥ 5 versus 0 serving/week | | | | | | | |
| 0.7 (0.4–1.1) | | | | | | | |

M men, W women

^a The results of margarine, butter and total milk and milk product were combined as the result for total dairy foods with a random effect model

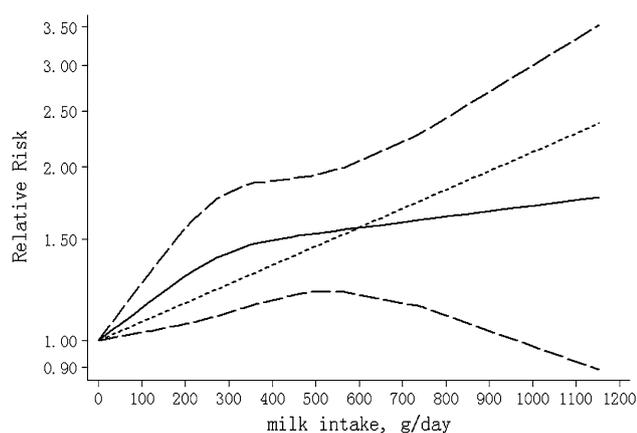


Fig. 2 The dose–response analysis between milk intake and risk of Parkinson’s disease. The *solid line* and the *long dash line* represent the estimated relative risk and its 95 % confidence interval. *Short dash line* represents the linear relationship

total dairy as a continuous variable [9, 11], but not for butter [7, 11] and yogurt [9, 11]. Therefore, the pooled results across study populations with different categories did not provide a precise estimation of PD risk associated with dairy foods and further studies are still needed to confirm the findings. Fermented milk products were believed to confer more beneficial effect, but its association with PD risk was still not observed [0.76 (0.32–1.80)] [7]. In addition, sour cream [1.7 (1.0–2.9)] [11], but not ice cream [0.8 (0.6–1.2)] [11] and 1.1 (0.8–1.5) [9], might be associated with PD risk. However, the limited data precluded a more robust estimation of the above-mentioned findings.

There was a clear difference in association between PD risk and milk and PD risk and other dairy products. However, pesticide residues like organochlorine pesticides herbicides and organophosphorus were detected in both milk, butter, cheese, and yoghurt, and milk also did not contain a higher concentration of pesticide residues than other dairy products [13–15]. The different effects of individual dairy products on serum uric acid levels are seldom investigated. The differences in urate levels between the extreme intake quintiles of milk [–0.25 (–0.40, –0.09)] and yogurt [–0.26 (–0.41, –0.21)] were significant, but the difference was not significant for cheese [–0.30 (–0.68, 0.08)] [4]. A significant and inverse association of urate levels with skimmed milk and low-calorie yoghurt was found, but not with low-fat yoghurt, full-fat yoghurt, semi-skimmed milk and full-fat milk [16]. While an acute urate-lowering effect of intact milk was observed in a randomised controlled crossover trial [5], trials on other dairy products with serum urate levels are lacking. Thus the difference in association between PD risk and

milk and PD risk and other dairy products needs to be confirmed, and the potential mechanism deserves to be explored.

Although observational studies cannot prove causality, results from this dose–response meta-analysis meet several of the Hill criteria for causation [13]: (1) Strength: the magnitude of this association is not negligible; (2) Consistency: increased risk of PD associated with milk intake was found in 4 of the 5 included prospective cohort studies, and low between-study heterogeneity was found; (3) Temporality: results from prospective cohort studies consist with an appropriate temporal relationship, in which the exposure precedes the outcome; (4) Biological gradient: the linear dose–response relationship meets with the biological gradient; (5) Plausibility and coherence: there is theoretical biological plausibility for causality in that dairy foods might increase the risk of PD. Milk consumption varies enormously with cultural and geographical differences in the world (http://en.wikipedia.org/wiki/List_of_countries_by_milk_consumption_per_capita, <http://charts.bin.com/view/1491>). Although limited studies showed a stronger risk estimate for studies conducted in USA than that in Europe, comparative studies are warranted in exploring the association of PD incidence with dairy consumption in future.

Although prospective cohort studies do not suffer from recall bias and are anticipated to be less likely to have selection bias relative to case–control studies, and only small or no between-study heterogeneity was found, other limitation should be also in mind. Misclassification of dairy foods and PD case could be of concern, and some participants might change their dairy foods habits during follow-up. Although results reflecting the greatest degree of control for potential confounders were extracted, residual confounding owing to measurement error or unmeasured confounding should be considered. Finally, in a meta-analysis of published studies, publication bias could be of concern because small studies with null results tend not to be published. Although no significant publication bias was detected in this meta-analysis, validity of publication bias test should be questioned because of small number of studies included.

In summary, dairy foods, especially for milk and cheese, might be associated with increased risk of PD, which still needs to be confirmed by well-designed prospective cohort studies, and the mechanism underlying this association needs to be elucidated further.

Acknowledgments This study was sponsored by National Natural Science Foundation of China (No. 31371024), and Shandong Provincial science foundation (ZR2009CM112).

Conflict of interest None.

References

1. Wirdefeldt K, Adami HO, Cole P, Trichopoulos D, Mandel J. Epidemiology and etiology of Parkinson's disease: a review of the evidence. *Eur J Epidemiol*. 2011;26(Suppl 1):S1–58.
2. Hernan MA, Takkouche B, Caamano-Isorna F, Gestal-Otero JJ. A meta-analysis of coffee drinking, cigarette smoking, and the risk of Parkinson's disease. *Ann Neurol*. 2002;52:276–84.
3. Van Maele-Fabry G, Hoet P, Vilain F, Lison D. Occupational exposure to pesticides and Parkinson's disease: a systematic review and meta-analysis of cohort studies. *Environ Int*. 2012;46:30–43.
4. Choi HK, Liu S, Curhan G. Intake of purine-rich foods, protein, and dairy products and relationship to serum levels of uric acid: the Third National Health and Nutrition Examination Survey. *Arthritis Rheum*. 2005;52:283–9.
5. Dalbeth N, Wong S, Gamble GD, et al. A cute effect of milk on serum urate concentrations: a randomised controlled crossover trial. *Ann Rheum Dis*. 2010;69:1677–82.
6. Shen C, Guo Y, Luo W, Lin C, Ding M. Serum urate and the risk of Parkinson's disease: results from a meta-analysis. *Can J Neurol Sci*. 2013;40:73–9.
7. Saaksjarvi K, Knekt P, Lundqvist A, et al. A cohort study on diet and the risk of Parkinson's disease: the role of food groups and diet quality. *Br J Nutr*. 2013;109:329–37.
8. Kyroziis A, Ghika A, Stathopoulos P, Vassilopoulos D, Trichopoulos D, Trichopoulou A. Dietary and lifestyle variables in relation to incidence of Parkinson's disease in Greece. *Eur J Epidemiol*. 2013;28:67–77.
9. Chen H, O'Reilly E, McCullough ML, et al. Consumption of dairy products and risk of Parkinson's disease. *Am J Epidemiol*. 2007;165:998–1006.
10. Park M, Ross GW, Petrovitch H, et al. Consumption of milk and calcium in midlife and the future risk of Parkinson disease. *Neurology*. 2005;64:1047–51.
11. Chen H, Zhang SM, Hernan MA, Willett WC, Ascherio A. Diet and Parkinson's disease: a potential role of dairy products in men. *Ann Neurol*. 2002;52:793–801.
12. Orsini N, Li R, Wolk A, Khudyakov P, Spiegelman D. Meta-analysis for linear and nonlinear dose-response relations: examples, an evaluation of approximations, and software. *Am J Epidemiol*. 2012;175:66–73.
13. Salem NM, Ahmad R, Estaitieh H. Organochlorine pesticide residues in dairy products in Jordan. *Chemosphere*. 2009;77:673–8.
14. Darko G, Acquah SO. Levels of organochlorine pesticides residues in dairy products in Kumasi Ghana. *Chemosphere*. 2008;71:294–8.
15. Mallatou H, Pappas CP, Kondyli E, Albanis TA. Pesticide residues in milk and cheeses from Greece. *Sci Total Environ*. 1997;196:111–7.
16. Zgaga L, Theodoratou E, Kyle J, et al. The association of dietary intake of purine-rich vegetables, sugar-sweetened beverages and dairy with plasma urate, in a cross-sectional study. *PLoS One*. 2012;7:e38123.