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REVIEW

Alcohol consumption and risk for Parkinson's disease: a systematic review and meta-analysis

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Abstract

The possibility that alcohol consumption should be considered as a "protective factor" for Parkinson's disease (PD) has been suggested by several case–control studies. However, other case–control studies and data from prospective longitudinal cohort studies have been inconclusive. We carried out a systematic review which included all the eligible studies published on PD risk related with alcohol consumption, and conducted a meta-analysis according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines. The systematic review was performed using two databases, and the meta-analysis of the eligible studies with the software Meta-Disc1.1.1. Heterogeneity between studies was tested with the Q-statistic. The meta-analysis included 26 eligible retrospective case–control studies (8798 PD patients, 15,699 controls) and 5 prospective longitudinal cohort studies (2404 PD patients, 600,592 controls) on alcohol consumption and PD. In retrospective case–control studies the frequency of PD patients never drinkers was higher and the frequency of heavy + moderate drinkers was lower [diagnostic OR (95% CI) 1.33(1.20–1.48) and 0.74(0.64–0.85)], respectively, when compared to healthy controls. In contrast, in prospective studies, the differences were not significant with the exception of a trend towards a higher frequency of non-drinkers in PD women and a significantly lower frequency of moderate + heavy drinkers in PD men in those studies which stratified data by gender. The present meta-analysis suggests an inverse association between alcohol consumption and PD, which is supported by the results of case–control studies but not clearly by prospective ones.

Keywords Parkinson's disease · Alcohol consumption · Meta-analysis · Risk factors

Introduction

Parkinson's disease (PD) is one of the most frequent neurodegenerative conditions. A huge number of studies investigating possible risk factors and protective factors for PD have been carried out during the last four decades. However, PD etiology remains unknown. Among the possible protective factors, exposure to smoking and alcohol, coffee and tea consumption, as part of lifestyle exposure, have been extensively studied using different designs, the results being inconclusive.

The first report on the issue of the possible relationship between alcohol consumption and the risk for PD by Baumann et al. [1] failed to show this association. However, many other further retrospective case–control studies described (despite the lack of uniformity in the study designs through the time, and the recognized possibility of recall bias) a higher frequency of never alcohol drinkers compared with ever alcohol drinkers in PD patients than in controls [2–15], and/or a lower frequency of the sum of moderate + heavy alcohol drinkers compared with the sum of low + no alcohol drinkers in PD patients than in controls [4, 10, 11, 16–19]. In contrast, other retrospective studies did not show any association between alcohol consumption and risk for PD [1, 20–36]. Several prospective longitudinal studies found, individually, non-significant differences in alcohol exposure between PD patients and controls [37–42].

Three previous meta-analyses, with several differences in the inclusion criteria and in the study design, have addressed

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the issue of alcohol consumption and its association with the risk for PD [43–45]. Ishihara and Bryne [43] included 13 case–control studies reported until September 2004, they used data from 2 preliminary studies in abstract form, and they measured alcohol intake as: 'ever vs. never'; 'yes vs. no'; ex- or current drinker vs. never drinkers; heavy or moderate intake vs. never drinkers. Noyce et al. [44] included 22 case–control studies published until March 2011 (they analyzed "drinking" vs. "non-drinking", although in several of the studies alcohol consumption was not a primary variable and was included as a potential confounder factor for adjustment for other study variables). Zhang et al. [45] included 24 case–control studies reported until October 2013 (two of them with insufficient information or reporting preliminary data), and analyzed a random-effect and a fixed-effect model. All these meta-analyses concluded that there was a significant trend towards lower alcohol consumption in PD patients than in controls, both in retrospective case–control studies and in prospective longitudinal studies. However, a "review of recent findings" without concomitant meta-analysis commented data on seven case–control studies, all of them reported between 2000 and 2014 and suggested a weak protective association between the alcohol consumption level and the risk for PD [46].

We performed a new systematic review and meta-analysis including reports until July 2018 and using stringent exclusion criteria. In addition, because several retrospective case–control studies [7, 9, 15, 16, 23, 26] and longitudinal studies [38, 40] analyzed alcohol consumption in PD patients and controls in men and women separately, we performed an analysis stratifying by gender.

Methods

Search strategy

Identification of eligible studies for this systematic review and meta-analysis was performed by crossing the term "Parkinson's disease" with "alcohol" and "ethanol", using the PubMed (2047 reports) and EMBASE (2066 reports) databases during the period ranging from 1966 to July 7, 2018. After a detailed revision of the contents of these reports, 48 studied the possible role of alcohol on the risk for PD [1–42, 47–52]. Seventeen studies were excluded from the meta-analysis because the following reasons: (A) Insufficient information (the authors gave the odds ratios and/or the *p* value of the association, but data regarding the frequency of exposure to alcohol were not available) [3, 8, 9, 28, 32, 37], (B) Reporting preliminary data and/or overlapping with other studies [20, 22, 36]; (C) Reporting data of alcohol consumption as mean ± SD of grams/day without giving information regarding the frequency of alcohol exposure [5, 19]; (D) Studies addressing history of alcohol abuse as a possible risk factor for PD [47–49]; (E) Studies addressing age of first contact with alcohol and age of onset of alcohol drinking habit [50] or analyzing only the age at onset of PD in relation with alcohol consumption [51]; (F) Studies reporting PD cases only without control group [52].

Therefore, only 31 eligible studies (26 case–control studies and 5 prospective longitudinal studies) were included in the final meta-analysis (Fig. 1).

Data extraction and analysis

The information extracted from each study included the journal, publication year, first author, number of cases and controls. We compared the frequencies of alcohol drinking habits in two ways: first, we compared the frequency of individuals who are never drinkers vs. individuals who consumed alcohol and, second, we compared the frequency of individuals who reported moderate + heavy alcohol consumption vs. individuals who are never drinkers + those reporting light alcohol consumption. To that end, and to overcome the lack of uniformity in the description of alcohol consumption across different studies, in this study we classified alcohol consumption considering quartiles of exposure. The statistical significance of the association of alcohol consumption with the risk of developing PD was analyzed for each study, and the associations were indicated as crude and diagnostic odds ratios (OR) with their corresponding 95% confidence intervals (CI). We estimated both fixed effects of the pooled OR, as well as random pooled OR effects, based on individual ORs. These analyses were done both with the total series and, whenever possible, stratifying by gender.

Statistical analysis

The software Meta-DiSc 1.1.1 (http://www.hrc.es/investigacion/ metadisc.html; Unit of Clinical Statistics, Hospital Ramón y Cajal, Madrid, Spain) [53] was used to perform the meta-analyses of the eligible case–control studies and longitudinal studies regarding the association between PD risk and alcohol consumption. The calculation of the global diagnostic OR was done using the Mantel–Haenszel method [54] when non-significant heterogeneity was observed, and the DerSimonian–Laird method [55] if statistically significant heterogeneity existed.

The heterogeneity between studies was assessed using the Q-statistic [56]. Heterogeneity was quantified using the I^2 metric [$(I^2 = (Q)df)/Q$], which is independent of the number of studies included in the meta-analysis [57]. I^2 takes values between 0 and 100% with higher values denoting a greater degree of heterogeneity. This value was considered significant when $P < 0.10$. The statistical power for the pooled sample of the eligible studies was also calculated.

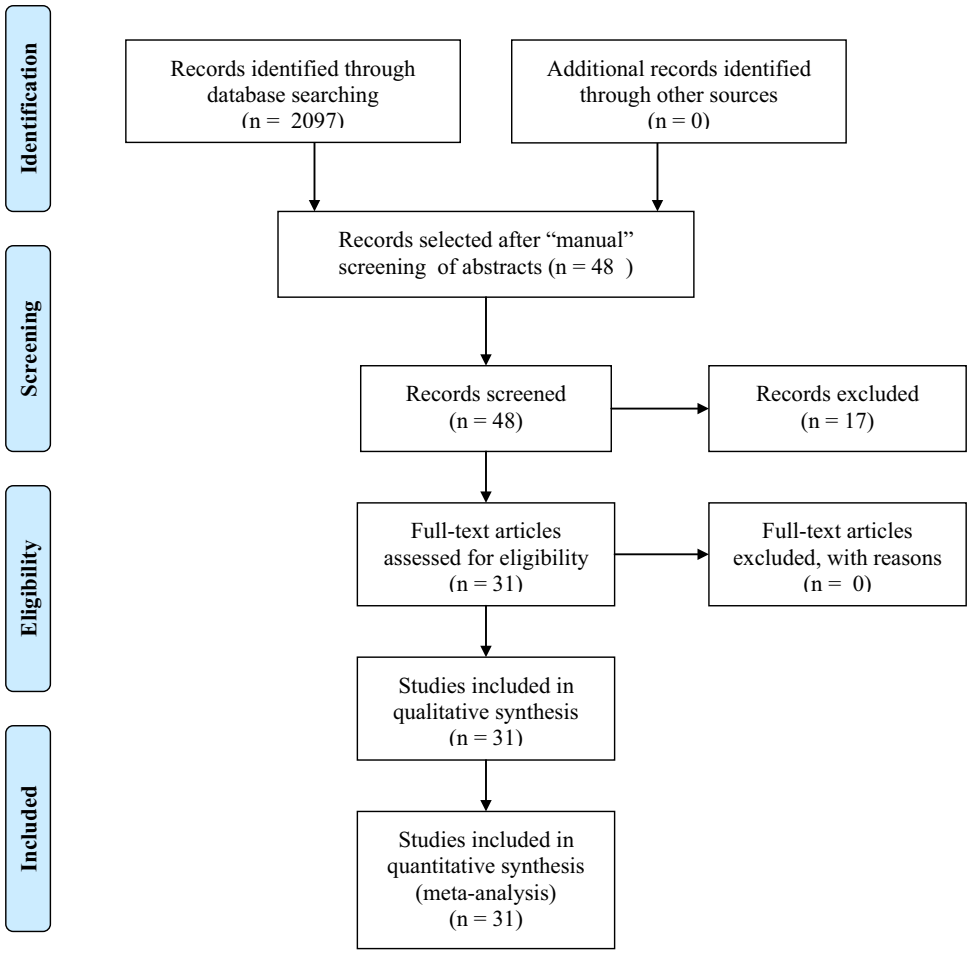

Fig. 1 Flowchart of the study selection

Ethical approval was not needed because this study is a systematic review and meta-analysis. PRISMA guidelines [58] were used to elaborate this work.

Results

The search using PubMed and EMBASE databases showed 26 case–control eligible studies comparing never vs. ever alcohol drinking, involving 8798 PD patients and 15,699 controls (Table 1; Fig. 2a). Ten studies showed a significantly higher frequency of never drinkers in the PD group, while the other 16 showed a lack of association. The pooled data showed a significantly higher frequency of never drinkers among PD patients, with a crude OR (95% CI) 1.55 (1.47–1.64) and a diagnostic OR (95% CI) 1.33 (1.20–1.48). This significantly higher frequency of never drinkers was observed as well when comparisons were stratified by gender, in the six studies which did so: the overall findings were as follows: Men—crude OR (95% CI) 1.29 (1.01–1.64); diagnostic OR (95% CI) 1.36 (1.06–1.75)—and women—crude OR (95% CI) 1.61 (1.32–1.97); diagnostic OR (95% CI) 1.2 (0.98–1.49). These six studies which stratified these results by gender, involved, respectively, 553 men PD patients/1820 men controls, and 533 women PD patients/1944 women controls (Table 2; Fig. 3a, b, respectively).

In contrast, in the 5 prospective longitudinal studies involving 2404 PD patients and 600,592 controls, the frequency of never drinkers did not differ significantly between PD patients and controls (Table 1; Fig. 2b). Only in two of these studies, the results were stratified by gender, and a trend toward a higher frequency of non-drinkers was found in PD women in comparison with control women (Table 2; Fig. 3c, d).

The search using PubMed and EMBASE databases showed 19 eligible case–control studies addressing alcohol consumption level, which involved 6843 PD patients and 12,733 controls (Table 3; Fig. 4a). When compared with controls, the frequency of heavy + moderate drinkers was significantly lower in PD patients in 8 studies, while other 11 did not find significant differences. The analysis of pooled data confirmed a lower frequency of heavy + moderate drinkers in the PD group, with a crude OR (95% CI) 0.84 (0.79–0.90) and a diagnostic OR (95% CI) 0.74 (0.64–0.85). This significantly lower frequency was observed as well for

Table 1 Case–control and prospective studies comparing frequency of never drinkers vs. ever drinkers between Parkinson's disease (PD) patients and controls

Author, year, [references]	Country	PD patients never drinkers/total series (%)	Controls never drinkers/total series (%)	Crude OR (95% CI)	Diagnostic OR (95% CI)
Case–control studies					
Baumann et al., 1980 [1], Haack et al., 1981 [20]	United States of America	129/237 (54.4%)	248/474 (52.3%)	1.09 (0.79–1.51); 0.595	1.09 (0.80–1.49)
Lang et al., 1982 [15]	England	10/125 (8%)	81/928 (8.7%)	0.91 (0.43–1.87); 0.786	0.91 (0.46–1.80)
Ho et al., 1989 [21]	Hong Kong	29/34 (85.3%)	83/105 (79.0%)	1.54 (0.49–5.13); 0.425	1.54 (0.53–4.43)
Jiménez-Jiménez et al., 1992 [16]	Spain	60/128 (46.9%)	122/256 (47.7%)	0.97 (0.52–1.52); 0.885	0.97 (0.63–1.48)
Wang et al., 1993 [2]	China	87/93 (93.5%)	151/186 (81.2%)	**3.36 (1.29–9.29); 0.006**	**3.36 (1.36–8.31)**
Morano et al., 1994 [23]	Spain	43/74 (58.1%)	74/148 (50.0%)	1.39 (0.76–2.53); 0.255	1.39 (0.79–2.44)
Hellenbrand et al., 1996 [17]	Germany	89/342 (26.0%)	85/342 (24.9%)	1.06 (0.74–1.52); 0.726	1.06 (0.75–1.50)
Liou et al., 1997 [4]	Taiwan	95/110 (86.4%)	173/240 (72.1%)	**2.45 (1.28–4.75); 0.003**	**2.45 (1.33–4.53)**
Gorell et al., 1999 [25]	United States of America	20/144 (13.9%)	53/464 (11.4%)	1.25 (0.69–2.24); 0.427	1.25 (0.72–2.17)
Fall et al. 1999 [6]	Sweden	69/111 (62.2%)	80/237 (33.8%)	**3.22 (1.97–5.30); < 0.001**	**3.22 (2.02–5.15)**
Benedetti et al., 2000 [26]	United States of America	43/187 (23.0%)	42/187 (22.5%)	1.03 (0.62–1.72); 0.902	1.03 (0.64–1.67)
Paganini-Hall, 2001 [18]	United States of America	109/394 (27.7%)	569/2317 (24.6%)	1.18 (0.92–1.50); 0.188	1.17 (0.92–1.49)
Behari et al., 2001 [27]	India	329/377 (87.3%)	318/377 (84.4%)	1.27 (0.83–1.96); 0.251	1.27 (0.84–1.92)
Checkoway et al., 2002 [28]	United States of America	86/210 (41.0%)	132/347 (38.0%)	1.13 (0.78–1.63); 0.495	1.13 (0.80–1.60)
Dong et al. 2003 [30]	China	85/114 (74.6%)	137/205 (66.8%)	1.46 (0.85–2.51); 0.151	1.45 (0.87–2.43)
Ragonese et al., 2003 [7]	Italy	78/150 (52.0%)	60/150 (40.0%)	**1.62 (1.00–2.64); 0.037**	**1.63 (1.03–2.57)**
Wirdefelt et al., 2003 [9]	Sweden	192/422 (45.5%)	820/2095 (39.1%)	**1.29 (1.05–1.61); 0.015**	**1.30 (1.05–1.60)**
Galanaud et al. 2005 [31]	France	164/247 (66.4%)	411/676 (60.8%)	1.27 (0.93–1.75); 0.120	1.27 (0.94–1.73)
Evans et al., 2006 [10]	England	33/106 (31.1%)	11/106 (10.4%)	**3.90 (1.75–8.85); < 0.001**	**3.90 (1.85–8.24)**
Dhillon et al., 2008 [11]	United States of America	60/140 (42.9%)	34/134 (25.4%)	**2.21 (1.28–3.81); 0.002**	**2.21 (1.32–3.69)**
Brighina et al., 2009 [12]	United States of America	280/893 (31.4%)	242/893 (27.1%)	**1.23 (1.00–1.52); 0.048**	**1.23 (1.00–1.51)**
Fukushima et al., 2010 [33]	Japan	115/214 (53.7%)	181/327 (55.4%)	0.94 (0.65–1.35); 0.713	0.94 (0.66–1.32)
Nicoletti et al., 2010 [34] and 2017 [36]	Italy	313/492 (63.6%)/	286/459 (62.3%)	1.06 (0.81–1.39); 0.676	1.06 (0.81–1.38)
Van der Mark et al., 2014 [35]	The Netherlands	104/444 (23.4%)	197/876 (22.5%)	1.05 (0.80–1.40); 0.702	1.05 (0.80–1.38)
Kenborg et al., 2015 [13]	Denmark	576/1448 (39.8%)	473/1542 (30.7%)	**1.49 (1.28–1.74); < 0.001**	**1.49 (1.28–1.74)**

Table 1 (continued)

Author, year, [references]	Country	PD patients never drinkers/total series (%)	Controls never drinkers/total series (%)	Crude OR (95% CI)	Diagnostic OR (95% CI)
Schernhammer et al.,2015 [14]	Denmark	648/1562 (41.5%)	525/1628 (32.2%)	**1.49 (1.29–1.73); < 0.001**	**1.49 (1.29–1.72)**
Total series		3846/8798 (43.7%)	5588/15,699 (35.6%)	**1.55 (1.47–1.64); < 0.001**	**1.33 (1.20–1.48)**
Prospective studies					
Hernán et al. 2003 [38]	United States of America	131/415 (31.6%)	39,550/135,674 (29.2%)	1.12 (0.91–1.39); 0.280	1.12 (0.91–1.38)
Ishihara-Paul et al. 2008 [39]	England	16/172 (9.3%)	1221/20,048 (6.1%)	1.58 (0.91–2.71) ; 0.080	1.58 (0.94–2.65)
Palacios et al., 2012 [40]	United States of America	221/605 (36.5%)	53,125/132,509 (40.1%)	0.86 (0.73–1.02) ; 0.074	0.86 (0.73–1.02)
Liu et al., 2013 [41]	United States of America	262/1113 (23.5%)	66,700/305,782 (21.8%)	1.11 (0.96–1.27) ; 0.164	1.10 (0.96–1.27)
Sääksjärvi et al. 2014 [42]	Finland	51/99 (51.5%)	3556/6579 (54.1%)	0.90 (0.60–1.37) ; 0.615	0.90 (0.61–1.34)
Total series		681/2404 (28.3%)	164,152/600,592 (27.3%)	1.05 (0.96–1.15) ; 0.274	1.04 (0.89–1.22)

Bold values indicates those p values with $p \leq 0.05$

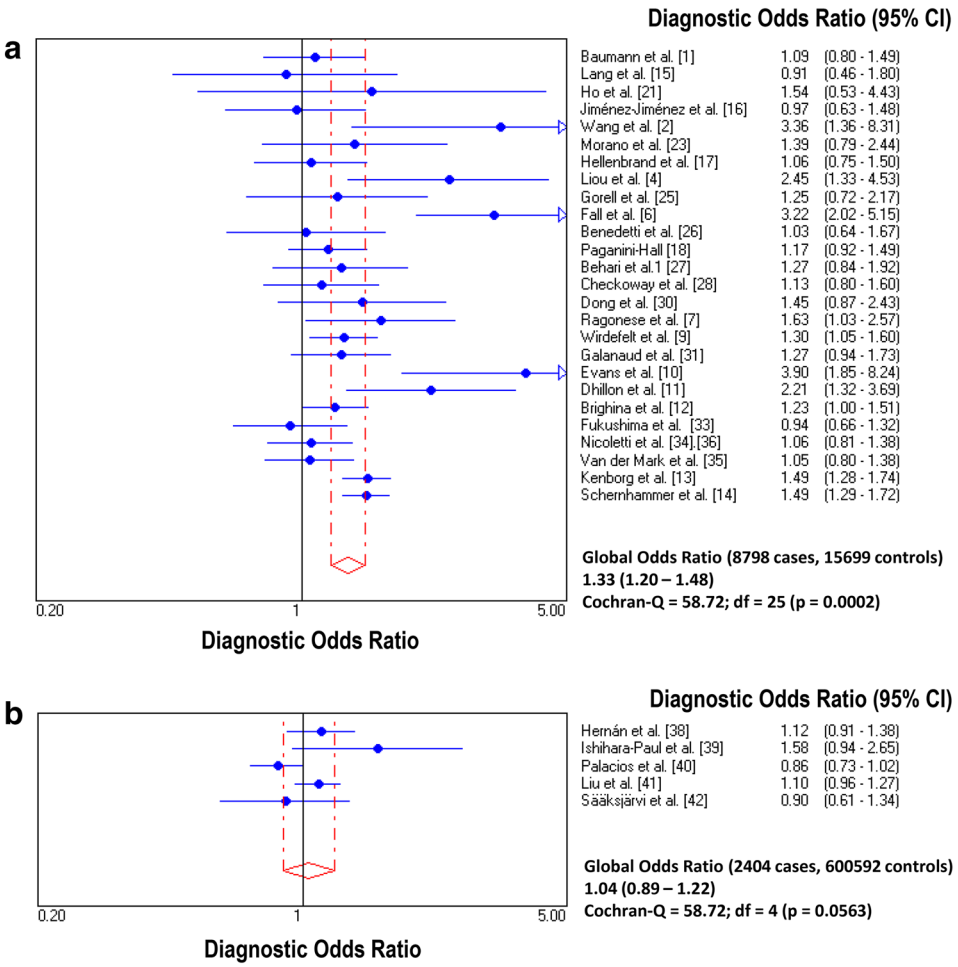

Fig. 2 Diagnostic odds ratios (OR) and 95% confidence intervals (CI) for each study and for pooled samples comparing never vs. ever alcohol drinking in the whole series of case–control studies (**a**) and in prospective longitudinal cohort studies (**b**)

Table 2 Case–control and prospective studies comparing frequency of never drinkers vs. ever drinkers between Parkinson's disease (PD) patients and controls stratified by gender

Author, year, [references]	Country	Male PD patients never drinkers/ total series (%)	Male controls never drinkers/ total series (%)	Crude OR (95% CI)	Diagnostic OR (95% CI)	Female PD patients never drinkers/total series (%)	Female controls never drinkers/ total series (%)	Crude OR (95% CI)	Diagnostic OR (95% CI)
Case–control studies									
Lang et al., 1982 [15]	England	5/61 (8.2%)	29/408 (7.1%)	1.17 (0.38–3.34); 0.760	1.17 (0.43–3.14)	5/64 (7.8%)	52/520 (10%)	0.76 (0.26–2.09); 0.578	0.76 (0.29–1.99)
Jiménez-Jiménez et al., 1992 [16]	Spain	14/68 (20.6%)	24/136 (17.6%)	1.21 (0.54–2.67); 0.612	1.21 (0.58–2.52)	46/60 (76.7%)	98/120 (81.7%)	0.74 (0.33–1.68); 0.430	0.74 (0.35–1.57)
Morano et al., 1994 [23]	Spain	9/33 (27.3%)	7/66 (10.6%)	**3.16 (0.94–10.84); 0.035**	**3.16 (1.06–9.46)**	34/41 (82.9%)	68/82 (82.9%)	1.00 (0.34–3.05); 1.000	1.00 (0.37–2.71)
Benedetti et al., 2000 [26]	United States of America	17/117 (14.5%)	14/117 (12%)	1.25 (0.55–2.85); 0.564	1.25 (0.59–2.67)	25/70 (35.7%)	29/70 (41.4%)	0.79/0.38–1.64; 0.489	0.79 (0.40–1.55)
Ragonese et al., 2003 [7]	Italy	19/68 (27.9%)	12/68 (17.6%)	1.81 (0.74–4.45); 0.154	1.81 (0.80–4.10)	59/82 (72%)	48/82 (58.5%)	1.82 (0.90–3.68); 0.072	1.82 (0.95–3.49)
Wirdefelt et al., 2003 [9]	Sweden	59/206 (28.6%)	245/1025 (23.9%)	1.28 (0.90–1.81); 0.150	1.28 (0.91–1.79)	133/216 (61.6%)	575/1070 (53.7%)	**1.38 (1.01–1.88); 0.035**	**1.38 (1.02–1.86)**
Total series		123/553 (22.2%)	331/1820 (18.2%)	**1.29 (1.01–1.64); 0.034**	**1.36 (1.06–1.75)**	302/533 (56.7%)	870/1944 (44.8%)	**1.61 (1.32–1.97); <0.001**	**1.21 (0.98–1.49)**
Prospective studies									
Hernán et al. 2003 [38]	United States of America	72/248 (29.0%)	11,120/47,119 (23.6%)	1.32 (1.00–1.76); 0.045	1.32 (1.01–1.74)	59/167 (35.3%)	28,436/88,555 (32.1%)	1.16 (0.83–1.61); 0.374	1.15 (0.84–1.59)
Palacios et al., 2012 [40]	United States of America	113/389 (29.0%)	18,976/58,388 (32.5%)	0.85 (0.68–1.07); 0.147	0.85 (0.68–1.06)	108/216 (50.0%)	34,329/74,121 (46.3%)	1.16 (0.88–1.53); 0.278	1.16 (0.89–1.51)
Total series		185/637 (29.0%)	30,096/105,507 (28.5%)	1.03 (0.86–1.22); 0.773	1.05 (0.68–1.63)	167/383 (43.6%)	62,765/162,676 (38.6)	**1.23 (1.00–1.51); 0.044**	**1.16 (0.96–1.40)**

Bold values indicates those p values with $p \leq 0.05$

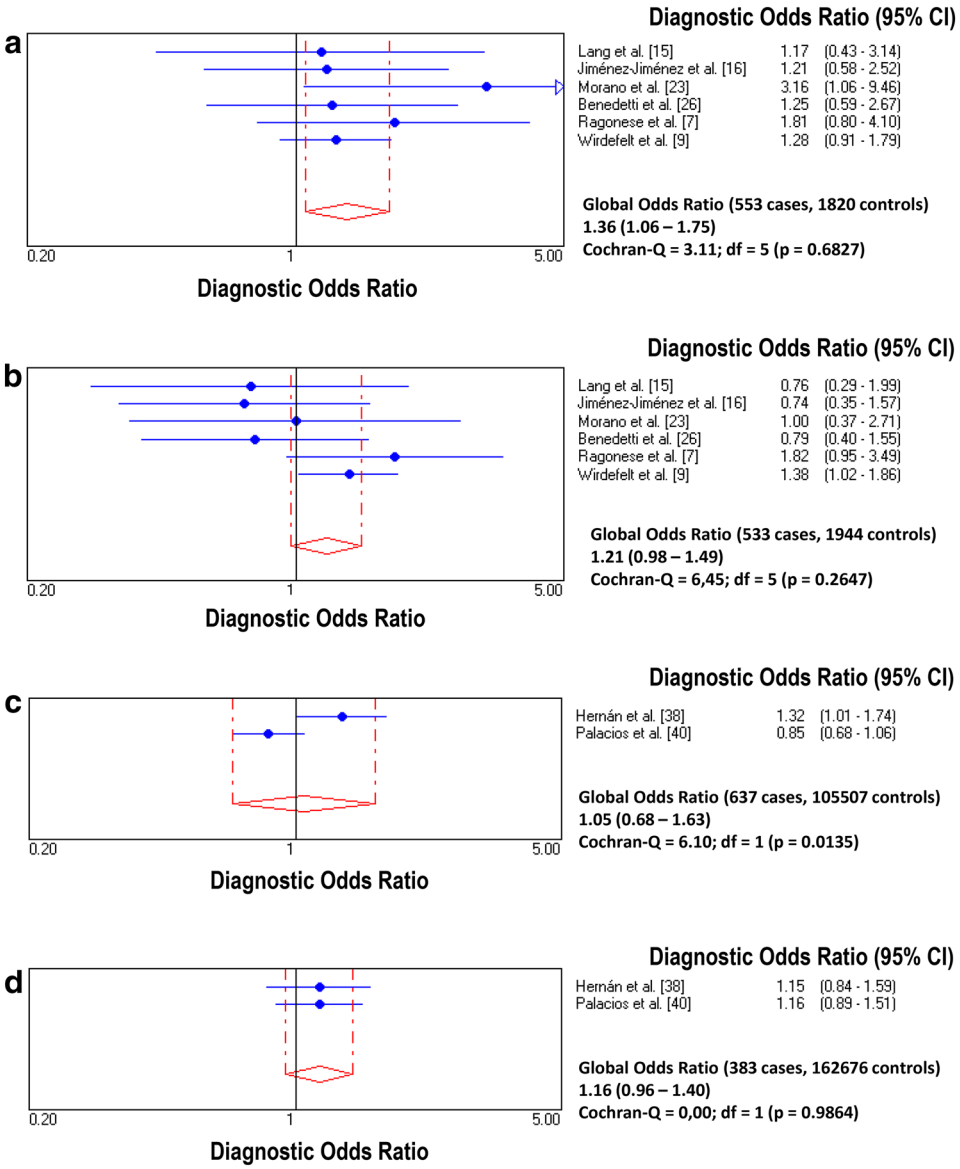

Fig. 3 Diagnostic odds ratios (OR) and 95% confidence intervals (CI) for each study and for pooled samples comparing never vs ever alcohol drinking stratified by gender in case–control studies (**a** men, **b** women) and in prospective longitudinal cohort studies (**c** men, **d** women)

men in the pooled data from 4 studies involving 367 PD patients and 1632 controls, with a crude OR (95% CI) 0.66 (0.50–0.88) and a diagnostic OR (95% CI) 0.44 (0.24–0.80), while in these studies the frequency of heavy + moderate drinkers among PD women ($n = 380$) when compared with control women ($n = 1792$), did not reach statistical significance (Table 4; Fig. 5a, b).

In the 4 prospective longitudinal studies involving 2232 PD patients and 580,634 controls, the frequency of heavy + moderate drinkers did not differ significantly between PD patients and controls (Table 3; Fig. 4b). However, the pooled data from the two studies in which the results were stratified by gender showed a significantly lower frequency of heavy + moderate drinkers in PD men when compared with PD controls, with a crude OR (95% CI) 0.74 (0.59–0.91) and a diagnostic OR (95% CI) 0.75 (0.62–0.91), while the differences were not significant in women (Table 4; Fig. 5c, d).

Discussion

The present systematic review and meta-analysis of case–control studies showed an inverse association between alcohol consumption and the risk of developing PD, both expressed as "never" vs. "ever" alcohol intake and when comparing heavy/moderate alcohol drinking with no/light alcohol consumption. These results are in agreement with those from the other three previous meta-analyses despite the several differences in the inclusion criteria and in the study designs which were summarized in the introduction [43–45]. The results regarding prospective longitudinal

Table 3 Case–control and prospective studies comparing frequency of patients with heavy–moderate vs. low–no alcohol consumption between Parkinson's disease (PD) patients and controls

Author, year, [references]	Country	PD patients moderate and heavy drinkers/total series (%)	Controls moderate and heavy drinkers/total series (%)	Crude OR (95% CI)	Diagnostic OR (95% CI)
Case–control studies					
Lang et al., 1982 [15]	England	9/125 (7.2%)	207/928 (22.3%)	**0.27 (0.13–0.56); < 0.001**	**0.27 (0.13–0.54)**
Jiménez-Jiménez et al., 1992 [16]	Spain	24/128 (19%)	89/256 (34.8%)	**0.43 (0.25–0.74); 0.001**	**0.43 (0.26–0.72)**
Morano et al., 1994 [23]	Spain	10/74 (13.5%)	36/148 (24.3%)	0.49 (0.21–1.10); 0.062	0.49 (0.23–1.04)
Mayeux et al., 1994 [24]	United States of America	39/150 (26%)	33/180 (18.3%)	1.57 (0.90–2.74); 0.094	1.57 (0.93–2.65)
Hellenbrand et al., 1996 [17]	Germany	132/342 (38.6%)	171/342 (50%)	**0.63 (0.46–0.86); 0.003**	0.63 (0.46–0.85)
Gorell et al., 1999 [25]	United States of America	89/144 (61.8%)	251/464 (54.1%)	1.37 (0.92–2.05); 0.104	1.37 (0.94–2.01)
Fall et al. 1999 [6]	Sweden	11/111 (9.9%)	56/237 (23.6%)	**0.36 (0.17–0.74); 0.003**	**0.36 (0.18–0.71)**
Benedetti et al., 2000 [26]	United States of America	58/187 (31.0%)	58/187 (31.0%)	1.00 (0.63–1.59); 1.000	1.00 (0.65–1.55)
Paganini-Hall, 2001 [18]	United States of America	159/394 (40.4%)	1110/2317 (47.9%)	**0.73 (0.59–0.92); 0.005**	**0.74 (0.59–0.91)**
Checkoway et al., 2002 [28]	United States of America	76/210 (36.2%)	143/347 (41.2%)	0.81 (0.56–1.17); 0.240	0.81 (0.57–1.15)
Ragonese et al., 2003 [7]	Italy	59/150 (39.3%)	74/150 (49.3%)	0.67 (0.41–1.08); 0.082	0.67 (0.42–1.05)
Wirdefelt et al., 2003 [9]	Sweden	38/422 (9%)	217/2095 (10.4%)	0.86 (0.59–1.25); 0.401	0.86 (0.60–1.23)
Evans et al., 2006 [10]	England	22/106 (20.8%)	38/106 (35.8%)	**0.47 (0.24–0.91); 0.015**	**0.47 (0.25–0.87)**
Dhillon et al.. 2008 [11]	United States of America	13/140 (9,3%)	34/134 (25.4%)	**0.30 (0.14–0.63) ; < 0.001**	**0.30 (0.15–0.60)**
Fukushima et al., 2010 [33]	Japan	53/214 (24.8%)	73/327 (22.3%)	1.15 (0.75–1.75); 0.511	1.15 (0.76–1.72)
Nicoletti et al., 2010 [34] and 2017 [36]	Italy	55/492 (11.2%)/	58/459 (12.6%)	0.87 (0.58–1.31); 0.488	0.87 (0.59–1.29)
Van der Mark et al., 2014 [35]	The Netherlands	148/444 (33.3%)	337/876 (38.5%)	0.80 (0.63–1.02); 0.067	0.80 (0.63–1.02)
Kenborg et al., 2015 [13]	Denmark	417/1448 (28.8%)	518/1542 (33.6%)	**0.80 (0.68–0.94); 0.005**	**0.80 (0.68–0.93)**
Schernhammer et al., 2015 [14]	Denmark	635/1562 (40.7%)	781/1628 (48%)	**0.74 (0.64–0.86); < 0.001**	**0.74 (0.65–0.85)**
Total series		2047/6843 (29.9%)	4284/12,723 (33.7%)	**0.84 (0.79–0.90); < 0.001**	**0.74 (0.64–0.85)**
Prospective studies					
Hernán et al. 2003 [38]	United States of America	65/415 (15.7%)	22,130/135,674 (16.3%)	0.95 (0.72–1.25); 0.721	0.95 (0.73–1.24)
Palacios et al., 2012 [40]	United States of America	95/605 (15.7%)	22,075/132,509 (16.7%)	0.93 (0.74–1.17); 0.529	0.93 (0.75–1.16)
Liu et al., 2013 [41]	United States of America	96/1113 (8.6%)	22,664/305,872 (7.4%)	1.18 (0.95–1.46); 0.122	1.18 (0.96–1.45)
Sääksjärvi et al. 2014 [42]	Finland	13/99 (13.1%)	1279/6579 (19.4%)	0.63 (0.33–1.16); 0.115	0.63 (0.35–1.13)
Total series		269/2232 (12.1%)	68,148/580,634 (11.7%)	1.03 (0.91–1.17); 0.644	1.00 (0.90–1.10)

Bold values indicates those p values with $p \leq 0.05$

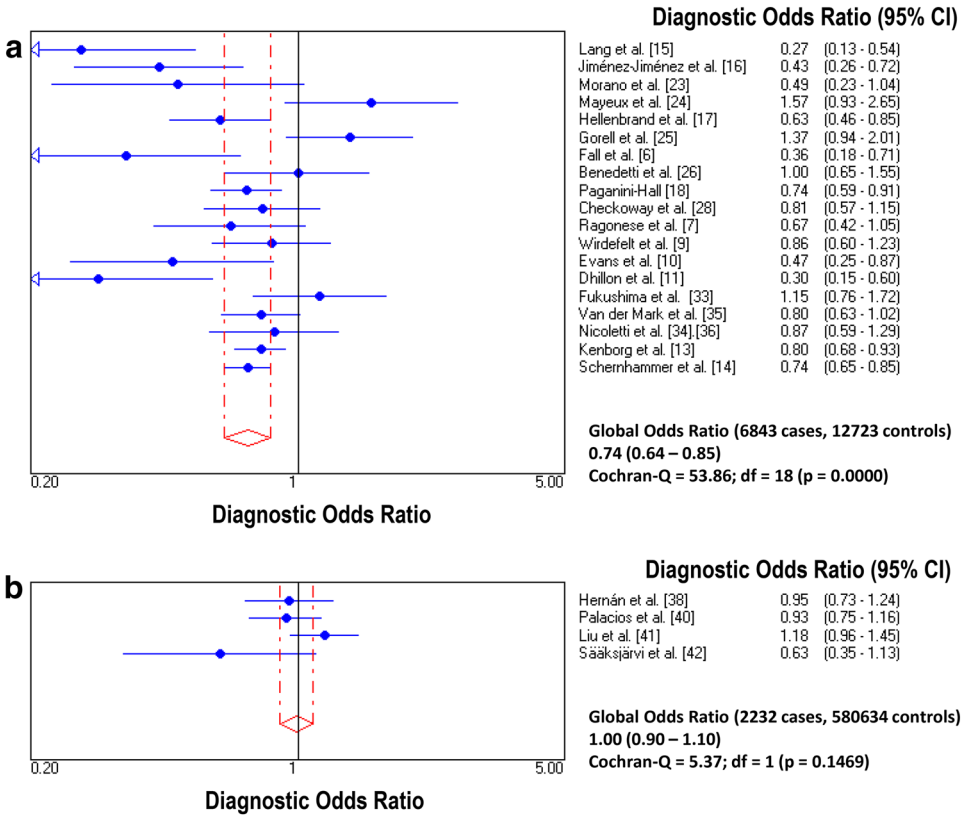

Fig. 4 Diagnostic odds ratios (OR) and 95% confidence intervals (CI) for each study and for pooled samples comparing heavy + moderate vs. lack of exposure + light alcohol consumption in the whole series of case–control studies (**a**) and in prospective longitudinal cohort studies (**b**)

cohort studies showed non-significant differences in alcohol consumption in the whole series of PD patients and controls. These results were in disagreement with those of other three meta-analyses which showed a significant trend towards lower alcohol consumption in PD patients than in controls [43–45]. Several differences could explain the discrepant results, such as differences regarding which type of study was considered to be a prospective longitudinal one. In our meta-analysis we did not include the study by Grandinetti et al. [37] because data regarding the frequency of exposure to alcohol were not available, despite the OR was given. The meta-analysis by Ishihara & Brayne [43] included a prospective study reported as preliminary data in abstract form. Zhang et al. [45] considered as prospective two case–control studies, one of them comparing the results of PD cases with six controls per patient selected among a cohort [19], and other that compared data from monozygotic twin pairs, one of them suffering from PD and other without PD, using as a control group the unaffected twin and other five healthy controls selected from a cohort [9]. Interestingly, in the two longitudinal studies in which both genders were analyzed separately, PD women showed a trend toward being non-drinkers than control women, while in the men, PD patients were less prone to be heavy or moderate alcohol drinkers than controls.

The reduced risk for PD found in many case–control studies could hypothetically raise the possibility of a "protective" effect of alcohol against PD development, but this possibility is far from being proved. The existence of a "premorbid personality" of PD patients trying to explain the differences in alcohol consumption between PD and controls has not been demonstrated either [59], although the inverse association of alcohol use with PD could reflect a low dopaminergic state which in turn should suppress addictive behavior. Interestingly, alcohol has several effects on the dopaminergic system (the main neurotransmitter system implied in the pathophysiology of PD) in experimental models, which include increase of dopamine release in the nucleus accumbens and in the amygdala, increase of dopaminergic neuron discharges in the ventral tegmental area and in the substantia nigra, and changes in the functioning of dopaminergic receptors in several brain areas [60].

One possibility to explain a lower trend towards alcohol consumption in PD patients could be hypothetically related to genetic factors. For example, rs1229984 single nucleotide polymorphism in the *alcohol-dehydrogenase 1B* (*ADH1B*) gene, seems to be implicated in the production of aversive effects to alcohol, and the carriers of the rs1229984T allele (which encodes the most active form of the ADH1B enzyme) show a trend towards lower alcohol consumption, possibly due to a more rapid conversion of alcohol to acetaldehyde [61]. To this respect, it has been described increased risk for PD in carriers of certain allelic variants of *alcohol-dehydrogenase A1 (ADHA1)* gene in one study [62], but not

Table 4 Case–control and prospective studies comparing frequency of patients with heavy–moderate vs low–no alcohol consumption between Parkinson's disease (PD) patients and controls stratified by gender

Author, year, [references]	Country	Male PD patients moderate and heavy drinkers/ total series (%)	Male controls moderate and heavy drinkers/ total series (%)	Crude OR (95% CI)	Diagnostic OR (95% CI)	Female PD patients moderate and heavy drinkers/total series (%)	Female controls moderate and heavy drinkers/ total series (%)	Crude OR (95% CI)	Diagnostic OR (95% CI)
Case–control studies									
Lang et al., 1982 [15]	England	9/61 (14.8%)	167/408 (40.9%)	**0.25 (0.11–0.54) ; < 0.001**	0.25 (0.12–0.52)	0/64 (0%)	42/520 (8.1%)	–	0.09 (0.01–1.44)
Jiménez-Jiménez et al., 1992 [16]	Spain	26/68 (38.2%)	83/136 (61%)	**0.40 (0.21–0.75); 0.002**	0.40 (0.22–0.72)	3/60 (5%)	1/120 (0.8%)	6.26 (0.56–159.90)	6.26 (0.64–61.55)
Morano et al., 1994 [23]	Spain	10/33 (30.3%)	36/66 (54.5%)	**0.36 (0.14–0.96); 0.023**	0.36 (0.15–0.88)	0/41 (0%)	0/82 (0%)	–	–
Wirdefelt et al., 2003 [9]	Sweden	31/205 (15.1%)	176/1022 (17.2%)	0.86 (0.55–1.32); 0.464	0.86 (0.57–1.30)	7/215 (3.3%)	41/1070 (3.8%)	0.85 (0.34–2.00); 0.685	0.84 (0.37–1.91)
Total series		76/367 (20.7%)	462/1632 (28.3%)	**0.66 (0.50–0.88); 0.003**	**0.44 (0.24–0.80)**	10/380 (2.6%)	84/1792 (4.7%)	0.55 (0.27–1.10); 0.074	0.69 (0.38–1.26)
Prospective studies									
Hernán et al. 2003 [38]		42/248 (16.9%)	11,547/47,119 (24.5%)	**0.63 (0.45–0.89); 0.006**	0.63 (0.45–0.88)	23/167 (13.8%)	10,583/88,555 (12.0%)	1.18 (0.74–1.86); 0.468	1.18 (0.76–1.83)
Palacios et al., 2012 [40]		60/389 (15.4%)	10,196/58,388 (17.5%)	0.86 (0.65–1.15); 0.291	0.86 (0.65–1.14)	35/216 (16.2%)	11,879/74,121 (16.0%)	1.01 (0.69–1.48); 0.943	1.01 (0.71–1.46)
Total series		102/637 (16%)	21,743/105,507 (20.6%)	**0.74 (0.59–0.91); 0.004**	**0.75 (0.62–0.91)**	58/383 (15.1%)	22,462/162,676 (13.8%)	1.11 (0.83–1.49); 0.449	1.07 (0.83–1.39)

Bold values indiicate those p values with $p \leq 0.05$

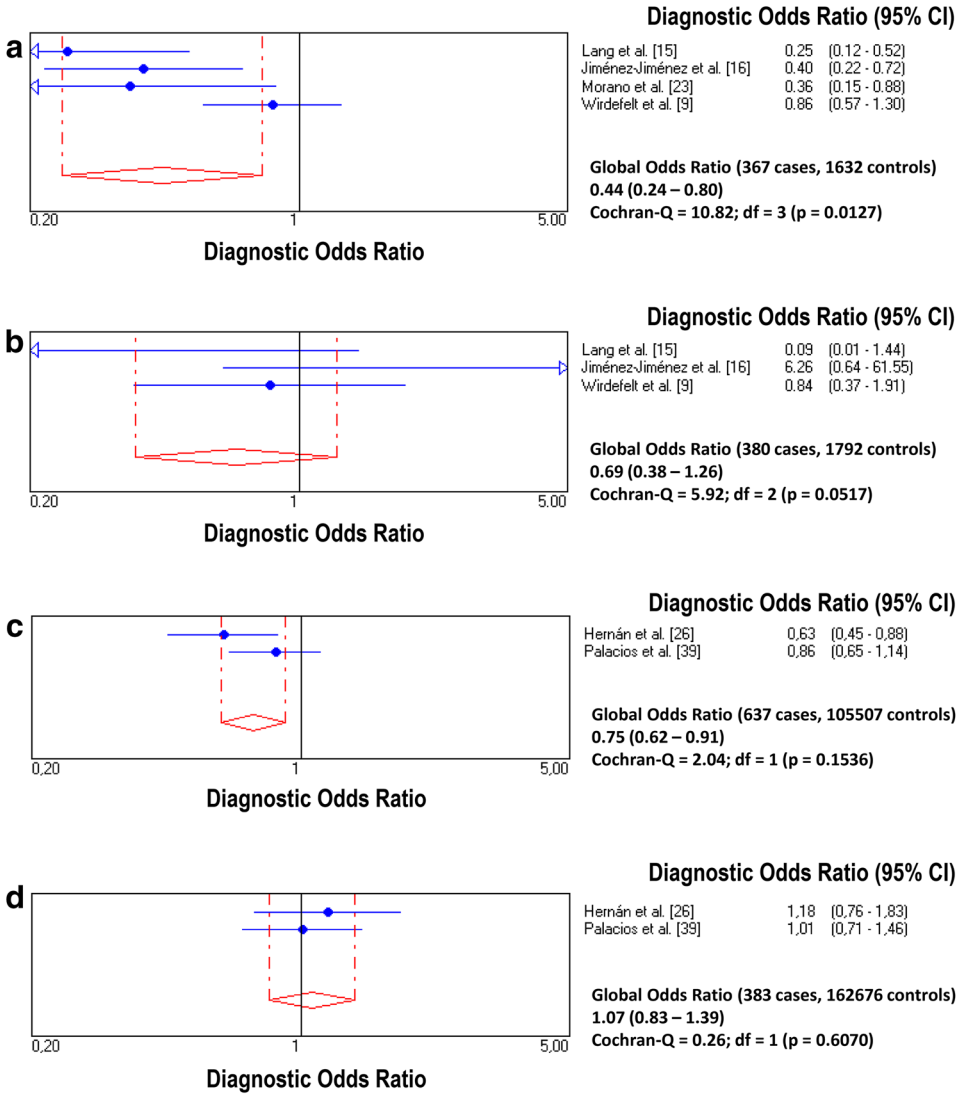

Fig. 5 Diagnostic odds ratios (OR) and 95% confidence intervals (CI) for each study and for pooled samples comparing heavy + moderate vs lack of exposure + light alcohol consumption stratified by gender in case–control studies (**a** men, **b** women) and in prospective longitudinal cohort studies (**c** men, **d** women)

in another one [63], association of the mutation G78Stop in the *ADH1C* with PD risk [64], and lack of association of *ADH1B* rs1229984 variants with the risk for PD in a Chinese study [65]. Interestingly, Adh1 and Adh4 knockout mice and Adh1/4 double knockout mice showed changes in dopaminergic function, suggesting a role of ADHs in the dopaminergic function [66, 67]. Together with ADHs, aldehyde-dehydrogenases (ALDH) play an important role in the metabolism of alcohol. The mRNA expression of ALDH1 has been found markedly decreased in the substantia nigra pars compacta of PD patients [68, 69], and the subpopulations of neurons within the substantia nigra pars compacta not expressing ALDH1A1 are more prone to neurodegeneration in alpha-synuclein transgenic mice, a murine model of PD [70]. Several studies have shown an association between certain single nucleotide polymorphisms in the *ALDH2* and the risk of developing PD [65, 71, 72], while others did not find such association [15, 37, 73].

In summary, the data obtained from the present meta-analysis showed, taking into account the considerations and limitations previously discussed, an inverse (protective?) association between alcohol consumption and risk for PD, which is supported by the results of case–control studies but not clearly by prospective longitudinal cohort studies (with the exception of gender-related differences in the latter). We suggest that an ideal kind of study trying to address the relationship between alcohol consumption and PD should involve a large cohort of subjects older than 50 years, free of PD at baseline, with a multicenter and prospective design and a long-term follow up (15–20 years). Alcohol consumption level should be assessed at baseline with a retest 1 year later, and the incidence of PD stratified by alcohol consumption levels and by gender should be calculated at the end of the study period.

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

Ethical standards The manuscript does not contain clinical studies or patient data.

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