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Review

Modifiable risk and protective factors in disease development, progression and clinical subtypes of Parkinson's disease: What do prospective studies suggest?

Daniele Belvisi[a,1], Roberta Pellicciari[b,1], Giovanni Fabbrini[a,c], Michele Tinazzi[d], Alfredo Berardelli[a,c,*], Giovanni Defazio[e]

[a] IRCCS Neuromed, via Atinense 18, 86077 Pozzilli, IS, Italy
[b] Department of Basic Medical Sciences, Neuroscience and Sense Organs, "Aldo Moro", University of Bari, Bari, Italy
[c] Department of Human Neurosciences, Sapienza University of Rome, Viale dell' Università 30, 00185 Rome, Italy
[d] Department of Neurosciences, Biomedicine and Movement Sciences, University of Verona, Via Casorati 43, 37131 Verona, Italy
[e] Department of Medical Sciences and Public Health, University of Cagliari, SS 554 bivio Sestu, 09042 Monserrato, CA, Italy

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ABSTRACT

Parkinson's disease (PD) is a neurodegenerative disorder whose pathogenesis depends on a combination of genetic and environmental factors. The aim of the present review was to provide an updated description of the findings emerging from prospective longitudinal cohort studies on the possible risk/protective factors underlying the development, progression and clinical subtypes of PD. We reviewed all the environmental, lifestyle, dietary, comorbid and pharmacological factors that have been investigated as possible modifiable protective/risk factors for PD by longitudinal studies. Only a few factors have the epidemiological evidence and the biological plausibility to be considered risk (pesticides, dairy products, β2-adrenoreceptor antagonists) or protective (smoking, caffeine and tea intake, physical activity, gout, vitamin E intake, non-steroidal anti-inflammatory drugs and β2-adrenoreceptor agonists) factors for PD. Caffeine intake and physical activity also seem to slow down the progression of the disease, thus representing good candidates for primary prevention and disease modifying strategies in PD. Possible modifiable risk factors of PD subtypes is almost unknown and this might depend on the uncertain biological and neuropathological reliability of clinical subtypes. The results of the present review suggest that only eleven risk/protective factors may be associated with the risk of PD. It may be possible to target some of these factors for preventive interventions aimed at reducing the risk of developing and the rate of progression of PD.

1. Introduction

Idiopathic Parkinson's disease (PD) is a chronic neurodegenerative disorder characterized by the progressive loss of dopaminergic neurons in the substantia nigra and in other neuronal systems (Kalia and Lang, 2016). Motor symptoms, such as tremor, rigidity and bradykinesia as well as a wide range of non-motor symptoms affecting various domains are hallmarks of the disease (Berardelli et al., 2013; Postuma et al., 2015; Goetz, 2011; Poewe et al., 2017). Clinical studies have also demonstrated that the presentation and the rate of progression of both motor and non-motor symptoms vary widely, thus raising the possibility that different subtypes of PD exist (Marras, 2015).

PD is now considered a multi-factorial disease (Kalia and Lang, 2016) that is due to a range of endogenous and exogenous factors. Genome-wide association studies have found that 26 independent single nucleotide polymorphisms are significantly associated with PD (Nalls et al., 2014), thereby highlighting a genetic contribution. Likewise, a large number of epidemiological investigations performed in recent decades have suggested that non-genetic endogenous and environmental factors also contribute to the etiology of PD. The existence of different risk factors may affect the development and varying progression rate of the disease, possibly explaining the different PD

Abbreviations: MMSE, mini mental state examination; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NSAID, non-steroidal anti-inflammatory drug; PD, Parkinson's disease; RR, relative risk; UPDRS, Unified Parkinson's disease rating scale

* Corresponding author at: Department of Human Neuroscience, IRCCS Neuromed, Sapienza University of Rome, Viale dell'Università 30, 00185 Rome, Italy.
E-mail address: alfredo.berardelli@uniroma1.it (A. Berardelli).

[1] These authors contributed equally to this paper.

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subtypes.

Although several potential endogenous and environmental factors have been investigated, only few risk factors have been identified consistently. One of the possible problems underlying the inconsistency of the data available in the literature is the design of the studies. For instance, while the majority of retrospective cross-sectional case-controls studies have suggested that hypertension is a protective factor for PD, prospective longitudinal cohort studies have not found any consistent correlation between hypertension and the development of PD. In addition, previous works have focused on risk/protective factors involved in the development of PD, leaving the risk/protective factors involved in the progression of PD and its subtypes largely unexplored.

The aim of the present review is to provide an updated description of the current literature on the possible risk/protective factors underlying the development, progression and clinical heterogeneity of PD by focusing exclusively on prospective longitudinal cohort studies. The strengths of the prospective design are attributable to the possibility of longitudinally assessing the effect of exposure over time, thus limiting the recall bias and the cause-and-effect bias that is known to affect case-control studies. This approach lends itself particularly to PD, a chronic long-lasting disease that is characterized by a prodromal phase of unknown duration. By adopting this approach, we aimed to highlight findings that can enhance our current knowledge of modifiable risk factors for PD. Identifying any modifiable predictive factors for PD and investigating how to effectively prevent them would obviously be highly relevant to the prevention and prognosis of this disease.

In this paper, therefore, we reviewed all the environmental, lifestyle and dietary factors as well as comorbidities and drugs that have been identified and investigated as possible modifiable protective/risk factors for PD by longitudinal investigations. We studied the possible effect of these factors on the development, progression and clinical subtypes of PD. Assessments were performed by taking into account the number of studies, the consistency of results and any methodological caveats that might affect the validity of the observations, such as the source and size of the study cohort, the duration of the follow-up, the number of incident PD cases and the management of potential confounders.

2. Methods

2.1. Search strategy and selection criteria

We performed a systematic database search on PubMed in order to identify all prospective studies that had examined the association between environmental factors and PD. The search strategy used the keywords Parkinson's disease or Parkinson's disease Progression or Parkinson's disease subtypes AND Risk factor OR Protective factor OR Education OR Occupation OR Marital status OR Socio-economic status OR Smoking OR Coffee OR Tea OR Physical activity OR Alcohol OR Food OR Diet OR Milk OR Dairy products OR Vitamin OR Macronutrients OR Protein OR Carbohydrates OR Fat OR Cholesterol OR Energy OR Comorbidities OR Surgery OR Trauma OR Infections OR Diabetes OR Hypertension OR Melanoma OR Cancer OR Non-steroidal anti-inflammatory agents OR Solvents OR Pesticides OR Dust OR Low-frequency electrical fields OR Low-frequency magnetic fields OR Rural living OR Oral contraceptives OR Drugs OR Diet OR Vitamins OR Risk factors. We only considered results coming from prospective cohort studies and/or from meta-analyses of prospective studies. Articles characterized by a different study design, by the use of non English language, and by uncertainties in PD diagnosis were excluded. According to these criteria we reviewed 91 studies and we rejected 465 studies. Factors analyzed by longitudinal studies dealing with onset, clinical type, and progression of PD are summarized in Fig. 1.

2.2. Data extraction

The full text of potentially eligible articles was closely examined independently by two investigators (G.D., R.P.) who extracted the following information from each study: country, cohort source and size, gender proportion of population, follow-up duration, assessment of risk factors, diagnostic criteria for PD, estimator of risk and 95% confidence interval, and study power. We attempted to weight the validity of studies that did not provide data on statistical power by examining those factors that contribute to the power of cohort studies, i.e. the source of the study cohort (which may have led to the type of exposure being misclassified or to the number of cases being underestimated), the size of the study cohort (which reflects the level of exposure) and the length of follow-up (a factor that is related both to the length of exposure and the development of a suitable number of affected subjects) and the adjustment for potentially confounding factors (Phillips and Pocock, 2004).

3. Risk/protective factors for PD

3.1. Environmental factors

A number of environmental risk factors for PD have been analyzed by prospective studies. However, data from multiple sources are available exclusively for pesticides, low-frequency magnetic fields and solvents (Table 1, supplementary material).

Of the eight studies that investigated exposure to pesticides, five revealed an increased risk of developing PD associated with such substances (Tuchsen and Astrup Jensen, 2000; Petrovitch et al., 2002; Baldi et al., 2003; Ascherio et al., 2006; Weisskopf et al., 2010). These five studies enrolled between 2792 and 143,325 individuals who were followed up for 5 to 27 years and provided 24 to 366 PD patients. No study provided information on specific factors that may affect pesticide exposure, such as the use of personal protective equipment. Details on specific pesticides were provided by one nested case-control study performed within the Finnish Mobile Clinic Health Examination Survey that examined serum biomarkers of organochlorine pesticides. The findings showed that exposure to dieldrin was associated with an increased risk of PD even though the effect of change or exposure to other less persistent pesticides could not be ruled out (Weisskopf et al., 2010). By contrast, another three studies performed on between 3124 and 120,852 individuals who were followed up for 17 to 29 years failed to find any significant association between occupational exposure to pesticides and PD (Feldman et al., 2011; Kenborg et al., 2012; Brouwer et al., 2015).

The cohort size and follow-up duration of the studies that found a positive correlation between pesticides and PD and those that did not were comparable. The studies in the latter group were, however, probably biased by methodological factors. For instance, one of these three studies that was based on the Swedish Twin Registry is unlikely to have been able to provide reliable data on any association between PD and occupational exposure to pesticides because twins usually share the same environment (Feldman et al., 2011). The other two studies did not instead focus on the development of PD but on standardized hospitalization rates and on deaths due to PD (Kenborg et al., 2012; Brouwer et al., 2015). As PD is largely diagnosed and managed in outpatient settings, hospitalization rates cannot be considered a reliable means of assessing the incidence of this disease, as suggested by the fact that only 28 incident PD patients were identified over 29 years of follow-up, nor can certificates of death capture all incident PD patients.

The possible association between exposure to high doses of low-frequency electrical and magnetic fields and PD was investigated in five studies (Table 1, supplementary material). Four of these studies, which were based on large populations followed up for several years, reported that the risk of PD among employees who were occupationally exposed to magnetic fields was not higher (Håkansson et al., 2003; Johansen, 2000; Savitz et al., 1998; Sorahan and Mohammed, 2014). It should be borne in mind that three of these studies did not assess morbidity but assessed the risk of PD as the primary or contributing cause of death

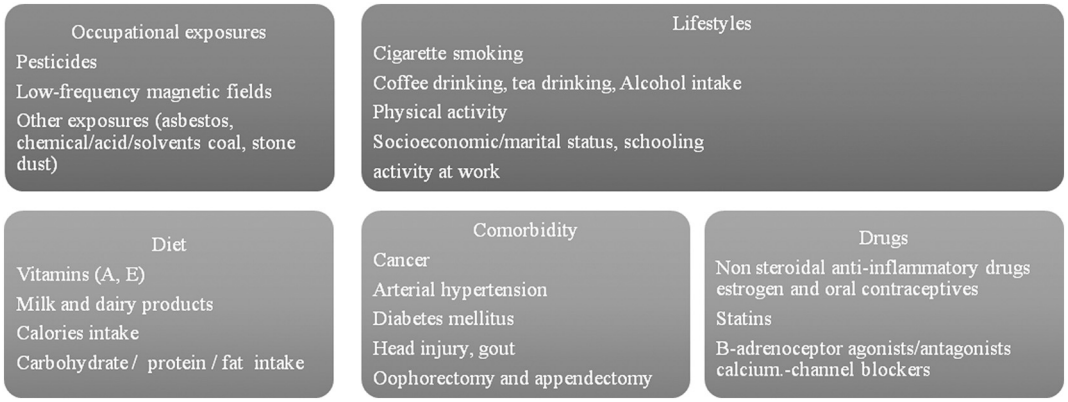

Fig. 1. Modifiable risk/protective factors for Parkinson's disease investigated by longitudinal studies.

which is likely to have limited the identification of PD patients (Håkansson et al., 2003; Savitz et al., 1998; Sorahan and Mohammed, 2014). Similarly, the only study that detected a significant association between PD and occupational exposure to magnetic fields assessed PD-related mortality (Brouwer et al., 2015). Even though the study performed by Brouwer et al. was performed in a large population (120,852 subjects) followed up for 17.3 years, the reliability of the findings yielded by that study was limited by the absence of a monotonic trend with either duration or cumulative exposure.

None of the three studies that investigated the relationship between solvents and PD detected any significant association (Brouwer et al., 2015; Feldman et al., 2011; Ascherio et al., 2006).

Other factors that have been investigated by one or, at most, two prospective studies include asbestos, chemicals/acids/solvents, coal, stone dust and other occupational exposures. No study provided evidence of a significant association between these factors and the development of PD.

In conclusion, studies assessing exposure to pesticides and low-frequency magnetic fields yielded contrasting results while studies focusing on other environmental exposures did not provide evidence of association (Fig. 2). Of note, the most methodologically robust studies point to a role of pesticides in the development of PD, a view that is further supported by the observation that most of the studies provided a similar estimation of risk despite differences in cohort size, follow-up duration and PD diagnosis. By contrast, studies on low-frequency magnetic fields suffered from bias that made results inconclusive. Likewise, further study is needed on other environmental exposures before we can consider the lack of association between PD and such factors reliable.

3.2. *Lifestyle factors*

Nine prospective studies assessed the relationship between cigarette smoking and the development of PD (Table 2, supplementary material). The majority of studies performed in ever, former and current smokers showed that cigarette smoking may play a protective role for PD. Indeed, there appears to be an inverse association between PD and the intensity and duration of smoking, which is more pronounced in current than in former smokers, decreases as the number of years after smoking has ceased increases, and is observed with a range of tobacco products (Grandinetti et al., 1994; Hernán et al., 2001; Paganini-Hill, 2001; Thacker et al., 2007; Tan et al., 2008; Sääksjärvi et al., 2008; Chen

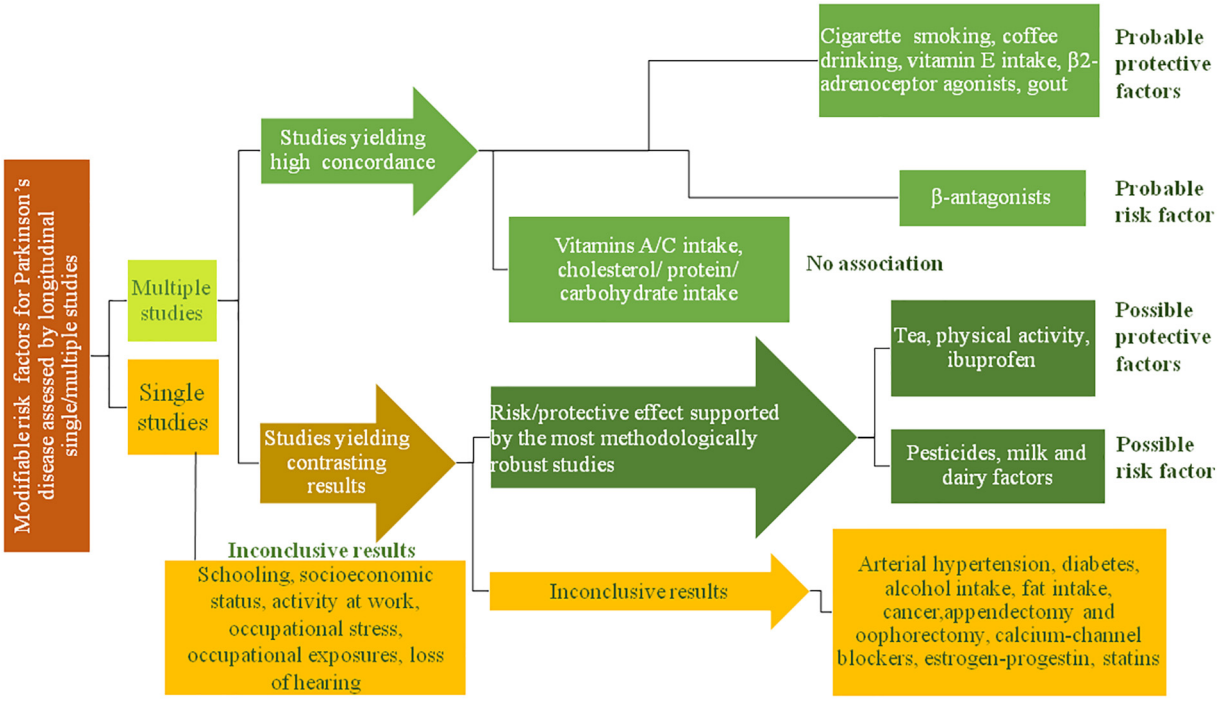

Fig. 2. Modifiable risk/protective factors for development of Parkinson's disease.

et al., 2009, 2010; Kyrozis et al., 2013) (Table 2, supplementary material). The inverse relationship between smoking and PD may depend either on the effect of nicotine on the central nervous system (Quik et al., 2012) or alternatively may reflect an inverse causality due to a premorbid personality trait making PD parients less inclined to start or continue to smoke (Evans et al., 2006).

Nine prospective studies clearly demonstrated that coffee is also likely to exert a protective effect against the development of PD, reducing this risk by approximately half (Ross et al., 2000; Paganini-Hill, 2001; Ascherio et al., 2001, 2004; Hu et al., 2007a; Sääksjärvi et al., 2008; Tan et al., 2008; Liu et al., 2012; Kyrozis et al., 2013) (Table 2, supplementary material). The validity and accuracy of these findings is supported by the similarity in the estimated risk of developing PD (the risk is roughly halved) reported in the majority of these studies, even after potentially confounding factors have been adjusted for. The inverse association between coffee and PD was found to be more pronounced in men than in women (Ascherio et al., 2004; Liu et al., 2012), probably as a result of an interaction with postmenopausal hormones (Ascherio et al., 2001).

The effects of tea consumption on PD risk have attracted much attention (Barranco Quintana et al., 2009) since tea components such as flavonoids, caffeine and theanine were reported to have a possible neuroprotective effect in animal models of PD. In line with these experimental observations, two prospective studies (Hu et al., 2007a; Tan et al., 2008) based on 29,335 and 63,257 individuals (who were followed up for 12 years) confirmed that consumption of tea (including black tea though not green tea) is inversely related to the development of PD. One prospective study based on a smaller population (Paganini-Hill, 2001) did not instead find any association between tea and PD (Table 2, supplementary material).

Six studies assessed the relationship between alcohol intake and PD. Four studies did not find any significant association between exposure and outcome (Grandinetti et al., 1994; Hernán et al., 2003; Tan et al., 2008; Palacios et al., 2012) whereas two suggested that alcohol may exert some degree of protection (Paganini-Hill, 2001; Liu et al., 2013) (Table 2, supplementary material). These contrasting results do not appear to be due to differences between studies in factors that contribute to study power. Although the power of one of the studies in which no association between alcohol intake and PD, which enrolled 8000 subjects but only yielded 58 PD patients over a 26-year-follow-up period (Grandinetti et al., 1994) was probably low, all the other studies in which no association was reported were characterized by large study cohorts (63,257 to 177,229 participants) and identified large numbers of PD patients (157 to 605).

When six prospective investigations assessed the relationship between physical activity and the incidence of PD, five indicated that physical activity might exert a protective role against PD (Chen et al., 2005a; Thacker et al., 2008; Xu et al., 2010; Yang et al., 2015; Kyrozis et al., 2013) (Table 2, supplementary material). These studies, which were based on 43,368 to 143,325 participants followed-up for 9 to 12 years, led to the identification of between 286 and 767 PD patients. One study did not instead find any inverse association between physical activity and PD (Logroscino et al., 2006), though it should be borne in mind that this study was characterized by a lower number of participants (10,714) as well as a lower PD diagnosis rate (101 patients), which are likely to have reduced its study power.

One large study performed on more than 300,000 subjects followed up for three years did not find any significant association between PD and socioeconomic (Caslake et al., 2014) and marital (Kyrozis et al., 2013) status (Table 2, supplementary material). Yet another two studies assessed schooling and intellectual work, two parameters that are related to socioeconomic status. Schooling did not appear to be related with the development of PD (Kyrozis et al., 2013) whereas intellectual work was found to be a risk factor for PD in a cohort of twin subjects (Valdés et al., 2014). Similarly, a recent study reported that occupational stress was positively associated with PD development (Sieurin et al., 2018).

In conclusion, studies assessing exposure to cigarette smoking and coffee were highly concordant in indicating a protective effect on PD development. Studies on tea, alcohol intake, and physical activity yielded contrasting results (Fig. 2). Of note, the most methodologically robust studies point to a protective role of tea and physical activity in the development of PD. By contrast, the findings of studies that assessed the relationship between alcohol intake and PD should be considered as inconclusive. Likewise, further study is needed on socioeconomic/marital status, schooling, intellectual work, and occupational stress before we can consider the association/lack of association between PD and such factors reliable.

3.3. Diet

Five prospective studies conducted on large cohorts of subjects that led to the diagnosis a relatively high number of PD patients indicated that dairy consumption and milk are likely to be associated with an increased risk of PD (Kyrozis et al., 2013; Chen et al., 2002, 2007; Park et al., 2005) (Table 3, supplementary material). Interestingly, studies on dairy consumption performed in the USA and Europe yielded a similar relative risk. Only one study did not find a significant association between PD and dairy products; however, the fact that this study was performed on a small cohort of subjects (about 4500 people) and yielded only 85 incident PD patients despite a very long follow-up (41 years) suggests that its study power was low (Sääksjärvi et al., 2013).

Several prospective studies have investigated the relationship between the intake of dietary vitamins and PD (Table 3, supplementary material). Evidence from studies based on large cohorts of subjects and yielding large numbers of PD patients suggested that the intake of vitamin A (Paganini-Hill, 2001; Tan et al., 2008) and C (Paganini-Hill, 2001; Zhang et al., 2002; Tan et al., 2008) was not associated with PD. By contrast, two studies reported that vitamin E has a protective effect. In 2002, Zhang et al. observed that the risk of PD was significantly lower among men and women with a high intake of dietary vitamin E (from foods only), and Tan et al. (2008) confirmed that a moderate intake of dietary vitamin E protects against PD. The two studies reported a similar relative risk.

On a global level, the dietary intake of calories, carbohydrates and proteins does not appear to be correlated with a greater or reduced risk for PD (see Table 3, supplementary material for references). These conclusions are based on studies based on large cohorts of subjects followed-up for several years and yielding large numbers of PD patients. Prospective studies on fat intake pointed to a more heterogeneous scenario, with fat intake being associated with an increased (Dong et al., 2014), decreased (Tan et al., 2008; Kyrozis et al., 2013; de Lau et al., 2005) or unchanged risk for PD (Chen et al., 2003a; Chen et al., 2007) in different studies. The findings that emerged from prospective studies designed to investigate cholesterol intake all excluded a strong relationship with PD (Chen et al., 2003a; Dong et al., 2014; de Lau et al., 2005; Kyrozis et al., 2013) (Table 3, supplementary material).

In conclusion, the findings that emerged from prospective studies designed to investigate the dietary intake of calories, carbohydrates, proteins, and cholesterol excluded a strong relationship with PD (Fig. 2). Studies on milk and dairy products yielded contrasting results but the most methodologically robust studies point to a protective role of this factor in the development of PD, a view that is further supported by the observation that studies from different countries provided similar estimation of risk. Finally, results of studies focusing on fat intake were inconclusive.

3.4. Comorbidities

Eighteen prospective studies assessed the relationships between the development of PD and comorbidities such as cancer (including

melanoma), arterial hypertension, diabetes mellitus, head injury, gout, oophorectomy and appendectomy (Table 4, supplementary material).

Prospective studies on cancer and melanoma have yielded conflicting results (Driver et al., 2007; Wirdefeldt et al., 2014; Fois et al., 2010; Freedman et al., 2016) despite most studies were based on more than 5–6 millions of participants and several thousands of ascertained PD patients (Table 4, supplementary material).

The findings from the five studies that investigated high blood pressure were inconsistent. Two studies (Simon et al., 2007; Tan et al., 2008) reported that the risk of PD was not significantly related to high blood pressure, while two other studies suggested that high blood pressure slightly increased the risk of PD (Lai et al., 2014; Qiu et al., 2011), at least in women with arterial hypertension (Qiu et al., 2011). One study instead reported that high blood pressure exerted a protective role against the development of PD (Paganini-Hill, 2001). All these studies differed in size (4976 to 171,879 participants), geographic origin (Finland, USA, Haway, Taiwan), and duration of the follow-up (10 to 22 years) of the cohort population. Interestingly, the study that was based on the smallest cohort of subjects was among those that reported that arterial hypertension was associated with an increased risk of PD, thereby suggesting that factors other than study power underlie the variability of the results. Geographic differences in the frequency of arterial hypertension in the general population and in the distribution of cardiovascular non-motor symptoms in PD patients might have contributed to these discrepancies.

Eight prospective studies investigated the relationship between PD and diabetes mellitus. Five studies (Paganini-Hill, 2001; Simon et al., 2007; Palacios et al., 2011; Tan et al., 2008; Lai et al., 2014), ruled out any association between the diabetes mellitus and PD. In these studies, the cohort size (13,799 to 171,879 participants), duration of the follow-up (10 to 22 years), and number of incident PD cases (157 to 530) likely led to sufficient study power. Conversely, three studies (Driver et al., 2008; Hu et al., 2007b; Xu et al., 2011) found a positive association between PD and diabetes mellitus. The study performed by Xu et al. was characterized by a large cohort size (288,662) and a high number of incident PD cases (1565) but the other two studies had similar statistical power of the five papers that did not find any association between PD and diabetes mellitus. Therefore, no definitive conclusions can be drawn.

Uric acid is a strong natural antioxidant. Uric acid reduces the burden of oxidative stress through several mechanisms including scavenging free radicals and chelating transition metals (Yeum et al., 2004; Bowman et al., 2010). In vivo and in vitro studies showed that uric acid might have a protective effect against dopaminergic neurons degeneration (Church and Ward, 1994; Duan et al., 2002). Accordingly, two studies performed on 7686 to 11,258 subjects followed up for 6 to 8 years found that gout exerted a protective effect against PD (Alonso et al., 2007; De Vera et al., 2008).

Two prospective studies designed to explore the possible effect of head injury and the development of PD instead excluded any such association (Lai et al., 2014; Fang et al., 2012), with one of those studies (Lai et al., 2014) also excluding any relationship between PD and loss of hearing (Lai et al., 2014).

In 2008, Rocca et al., 2008 observed that both unilateral and bilateral oophorectomy performed prior to menopause in 2327 women followed up over 28 years was associated with an increased risk of PD. The finding was not confirmed, however, in 121,701 subjects enrolled in the Nurses' Health Study who were followed up for 22 years (Simon et al., 2009). Lastly, three studies found either no association or a weak association between PD and appendectomy (Marras et al., 2016; Svensson et al., 2016; Palacios et al., 2018).

In conclusion, the findings that emerged from prospective studies designed to investigate diabetes and head trauma were consistent with a lack of association with PD, while studies assessing gout were concordant in indicating a protective effect on PD development (Fig. 2). Results of studies focusing on cancer, arterial hypertension, oophorectomy and appendectomy were inconclusive.

3.5. Drugs

The drugs that have been investigated as possible risk factors for idiopathic PD are non-steroidal anti-inflammatory drugs (NSAIDs), calcium channels blockers, estrogen and oral contraceptives, statins, β-adrenoceptor agonists and antagonists and (Table 5, supplementary material).

Six studies based on a prospective design followed up between 6512 and 2,005,552subjects to assess whether the use of NSAIDs affects the risk of PD (Chen et al., 2003b,Chen et al., 2005b; Hernan et al., 2006; Bornebroek et al., 2007; Gao et al., 2011). Regular use of non-aspirin NSAIDs reduced the risk of developing PD whereas aspirin exerted a negligible protective role (Chen et al., 2003b; Chen et al., 2005b; Hernan et al., 2006). Another prospective study showed that ibuprofen, though not aspirin, was associated with a lower risk of PD (Chen et al., 2005b). Likewise, when Gao et al., 2012 investigated various NSAIDs, only ibuprofen was found to be inversely correlated with PD. Bornebroek et al. (2007) and Driver et al. (2011) did not however confirm the correlation with ibruprofen and excluded any association between NSAIDs and PD, though it should be borne in mind that their studies were the ones with the smallest sample size (Table 5, supplementary material).

Three controlled prospective studies investigated calcium channel blockers. Two studies performed on 5278 to 17,329 participants did not find any association between this category of drugs and PD (Louis et al., 2009; Simon et al., 2010), whereas the third (Pasternak et al., 2012) reported an association between calcium channel blockers and a reduced risk of PD, particularly in older patients, though the reduction in this last study, which was performed on a very large cohort (2,573,281 subjects), was slight (RR = 0.71).

The prospective studies in the literature all agree that the intake of β-adrenoceptor agonists may act as a protective factor and that the intake of β-adrenoceptor antagonists may act as a risk factor for PD development (Mittal et al., 2017; Gronich et al., 2018; Koren et al., 2019). In line with these studies, Mittal et al. (2017) reported that the β2-adrenoreceptor is a regulator of the transcription of α-synuclein gene in animal models.

With regard to findings regarding a possible association between exposure to estrogen-progestin treatment and PD (Ascherio et al., 2004; Simon et al., 2009; Rugbjerg et al., 2013; Liu and Wang, 2014), two studies reported that estrogen replacement cancelled the protective effect of caffeine (Ascherio et al., 2004) and cigarette smoking (Simon et al., 2009) on PD development.

The prospective studies on a possible relationship between PD and statins were inconclusive, as demonstrated by contrasting reports of no association, of a slightly reduced risk or of an increased risk resulting from this association (de Lau et al., 2007; Wolozin et al., 2007; Friedman et al., 2013; Huang et al., 2015)

In conclusion, studies were concordant in indicating that ibuprofen and β-adrenoceptor agonists may act as protective factors and that β-adrenoceptor antagonists may act as a risk factor for PD development. Results of studies on calcium-channel blockers, estrogen-progestin and statins were inconclusive (Fig. 2).

4. Risk/protective factors for PD clinical subtypes

We found only one prospective study on the risk factors for PD clinical subtypes. In the Norwegian Park West study, Skeie et al. (2010) followed 212 incident PD patients and 175 age- and gender-matched controls for 28 months. The authors observed that the combination of alcohol and smoking was inversely associated with the development of the postural instability-gait disorder subtype of PD. Conversely, the incidence of patients with the tremor-dominant PD subtype was not affected by any of the risk factors investigated.

5. Risk/protective factors for PD progression

Few studies have assessed the association between risk factors for PD and disease progression. In 2019, Paul et al., 2019 performed a prospective cohort study designed to investigate the possible effects of lifestyle factors on PD motor and cognitive impairment, progression and survival. The authors, who included 360 PD patients (mean follow-up: 5.3 years), found that coffee consumption and a history of competitive sports slowed both motor and cognitive decline as assessed by the Hoehn and Yahr scale and Mini-Mental State Examination (MMSE), respectively; coffee was also found to reduce mortality. By contrast, current cigarette smoking and heavy alcohol consumption were associated with a faster motor and cognitive decline.

Eight randomized controlled trials with a follow-up ranging from 4 weeks to 2 years investigated the possibility that creatine, CoQ10 or its analogues exert protective effects on the progression of PD motor symptoms (cited in Liu and Wang, 2014), though this hypothesis was not supported by data on longitudinal changes in motor symptom severity as assessed by the UPDRS-III (Liu and Wang, 2014).

The effects exerted by comorbidities on PD progression have also been investigated. A secondary analysis of data in 1022 out of 1741 participants in the National Institute of Neurological Disorders and Stroke Exploratory Clinical Trials in Parkinson's disease Long-Term Study, showed that, over a 3-year follow-up period, PD patients who met the clinical criteria for metabolic syndrome experienced a greater increase in motor symptom severity, as assessed by an annual increase in the total UPDRS score, than PD patients without metabolic syndrome (Leehey et al., 2017). More recently, Mollenhauer et al., 2019 investigated possible baseline risk factors for PD progression in 135 de novo PD patients. The authors observed that symptoms worsened over 4 years in PD, with an annual change of 1.8 points on the Unified Parkinson's disease rating scale (UPDRS) part III and 0.2 points on the MMSE. A worse progression of motor symptoms in PD was also associated with male sex, a drop in orthostatic blood pressure, diagnosis of coronary artery disease, arterial hypertension and high serum uric acid levels. Cognitive decline was associated with previous heavy alcohol abuse, current diagnosis of diabetes mellitus, arterial hypertension and high density lipoprotein, cholesterol as well as high glucose levels.

Lastly, two longitudinal clinical trials investigated the relationship between serum urate concentrations and PD progression. Schwarzschild et al. (2008) prospectively evaluated 804 early PD patients enrolled in the PRECEPT study, a clinical trial aimed at assessing the neuroprotectant potential of CEP-1347 (follow up: 21.4 months). The primary study endpoint was progression to a level of clinical disability requiring dopaminergic therapy. The adjusted hazard ratio of the endpoint being reached declined as baseline concentrations of urate increased, an association that was markedly stronger in men than in women. In 2009, Ascherio et al., 2009 measured serum and cerebrospinal fluid concentrations of urate in 800 PD patients enrolled in the DATATOP trial and followed up for 13 years. The authors of that study confirmed that the progression of PD disability (defined as clinical disability requiring levodopa therapy) declined as serum urate concentrations increased.

6. Discussion

In this paper, we reviewed prospective longitudinal studies on risk and protective factors for PD. Several factors were investigated by single studies and were not found to be associated with PD. We will discuss only those factors that were investigated by multiple studies so as to be able to assess the level of concordance across studies. Although the findings from some of these studies were concordant, the majority of the factors examined in different studies yielded discordant results.

6.1. Probable, possible and uncertain risk/protective factors for PD

To understand the strength of the associations between PD and those factors better, we have stratified the aforementioned risk factors into three groups, probable, possible and uncertain factors (Fig. 2). The first group includes factors for which studies yielded a high level of concordance: cigarette smoking and coffee drinking, vitamin E intake, β2-adrenoceptor agonists, and gout which exerted a protective effect; cholesterol and protein and carbohydrate intake, which were not found to be associated with PD; lastly, β-adrenoreceptor antagonists, which was associated with an increased risk of PD. The second group includes possible risk/protective factors for which studies yielded contrasting results.

We determined whether these discrepancies might be ascribable to methodological differences (source of the study, size of the study cohort, length of follow-up, adjustment for potentially confounding factors). We found that tea, pesticides, physical activity, intake of milk and dairy products, and some NSAIDs, including ibuprofen, were significantly associated with PD in those studies that were based on a larger cohort size and longer follow-up though not those based on smaller cohorts and a shorter follow-up. Since the size of the study cohort and the length of follow-up make an important contribution to study power, it is likely that the lack of any association observed in the latter group of studies might be due to their lower statistical power.

The findings concerning other risk factors, such as arterial hypertension, diabetes mellitus, alcohol intake, fat intake, cancer, oophorectomy, appendectomy, calcium-channel blockers, estrogen-progestin, and statins were discrepant, though no substantial methodological differences emerged between studies that reported significant associations and those that did not. The contrasting results in this group of studies are therefore likely to be due not so much to differences in study power between studies as to differences in other study characteristics that may be difficult to detect. Since estimators of risk were adjusted for potentially confounding variables in the majority of the studies we examined, this factor is unlikely to have contributed to discrepancies across studies. In addition, although the prospective studies on factors such as melanoma and arterial hypertension did point to significant associations, it was direct in some cases and inverse in others. The evidence regarding the factors examined in the third group of studies was instead generally inconclusive.

To sum up, the prospective studies we examined suggest that pesticides, cigarette smoking, coffee, tea, β2-adrenoreceptor agonists/antagonists, physical activity, intake of milk and dairy products, vitamin E, gout and some NSAID, such as ibuprofen, can be considered as probable or possible risk/protective factors for PD. The eleven probable or possible risk/protective factors for PD may be considered as independent factors given that were identified in prospective studies that in the majority of cases verified the influence of some potential confounders by using multivariate analysis. By the way, no studies has yet evaluated all possible risk/protective confounding factors for PD in the same population and it is, therefore, not possible to exclude influence from other potentially confounding variables that were not considered in the previous studies. Evidence from prospective studies on other factors is lacking or remains inconclusive.

6.2. The biological plausibility of risk/protective factors for PD

The 11 factors which have strong epidemiological evidence as risk/protective factors for PD are biologically plausible. The active metabolite of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), whose structure is similar to that of the herbicide paraquat, is known to be involved in the pathogenesis of a subacute form of parkinsonism. In vitro and in vivo studies have shown that some pesticides exert a toxic effect on the dopaminergic pathways (Di Monte et al., 2002; Brown et al., 2006), with recent data suggesting that there may be a gene-based susceptibility to these effects (Gao et al., 2011; Elbaz and Tranchant, 2007). For instance, Elbaz et al. observed that the relationship between pesticide exposure and PD was approximately two times stronger in subjects who were CYP2D6 poor metabolizers than in

those who were not (Elbaz et al., 2004). The neuroprotective role of cigarette smoking and coffee might be related to the marked effects exerted by nicotine and caffeine on the central nervous system. Indeed, caffeine is an adenosine receptor antagonist that prevents the development of PD in animal models (Bagga et al., 2016). Nicotine (Quik et al., 2012) as well as tea components such as flavonoids and theanine have been shown to exert a neuroprotective effect in animal models of PD (Ascherio and Schwarzschild, 2016). Theanine can inhibit the transport of glutamine and regulate the glutamate-glutamine cycle formed between neurons and astrocytes (Kakuda et al., 2008), that is relevant for neuroprotection (Tani et al., 2014). In animal models, intensive physical exercise has been associated with neuroprotective and neurorestorative effects in the nigrostriatal dopaminergic system (Ahlskog, 2011; Petzinger et al., 2013). In particular, physical exercise would contribute through an increased concentration of BDNF (Wu et al., 2011) toward reconstituting the function of the basal ganglia involved in the motor command by the adaptive mechanisms of dopamine and glutamate neurotransmission (Speelman et al., 2011). A growing body of evidence suggests that the prodromal phases of PD begin in the gut and subsequently affect brain areas (Poewe et al., 2017; Houser and Tansey, 2017; Rocha et al., 2015). Recent data also strongly support a role of peripheral inflammatory/immune responses in PD (Rocha et al., 2015), thereby suggesting that the initial inflammatory cascade in PD initiates in the gut before being exacerbated by aging-related inflammation. This in turn raises the possibility that diet compounds with anti-inflammatory effects could be included in therapeutic protocols for PD. Vitamin E is a powerful antioxidant, whose neuroprotective effects have been demonstrated in multiple experimental models (Sharma and Nehru, 2013). Vitamin E may exert a protective effect on PD by intervening in mitochondrial (Hornsby, 1989) and lysosome (Marín et al., 2014) function and it has been recently demonstrated that administration of vitamin E was able to revert synaptic plasticity abnormalities in PINK1 −/− mice (Schirinzi et al., 2019). Similarly, the mechanisms behind the potential protective effect of gout on PD may depend on the antioxidant properties of uric acid (De Vera et al., 2008). In MPTP model of PD, uric acid completely prevented the death of the dopaminergic cells induced by homocysteine plus rotenone or iron (Duan et al., 2002). Concordantly, it has been suggested that the increased risk of PD associated with milk and dairy consumption is due to the urate-lowering effects of dairy products. NSAIDs might help to delay or prevent the onset of clinical PD by suppressing the pro-inflammatory responses of microglia associated with neuronal degeneration. Ibuprofen is one NSAID that has specific protective properties related, among other things, to the activation of PPAR-gamma, a proposed therapeutic target for PD. In addition, ibuprofen protects dopaminergic neurons against glutamate toxicity in vitro (Casper et al., 2000). Lastly, molecular and immunological data suggest that adrenergic stimulation may reduce both α-synuclein deposition and pro-inflammatory / neurotoxic molecule release, thereby lending support to epidemiological studies whose findings have suggested that long-term exposure to the agonist salbutamol protects against the development of PD whereas long-term exposure to the antagonist propranolol increases the risk of PD (Mittal et al., 2017).

6.3. Risk/protective factors for PD subtypes

Since genetic determinants seem to play a limited role in differentiating PD subtypes (Fereshtehnejad et al., 2017) and the clinicopathological correlation of PD subtypes is unclear (Espay and Marras, 2019), it is conceivable that a complex interplay of modifiable environmental factors underlies the various subtypes. Although the observation that PD is a heterogeneous syndrome was reported decades ago (Helmich et al., 2012; Zetusky et al., 2012; Jankovic et al., 1990), only recently the scientific community started focusing on subtyping PD patients. In addition, the identification of the subtypes strictly depends on the variables considered. Recent approaches have combined a number of different motor and non-motor signs (Fereshtehnejad et al., 2017), thus leading to the identification of different subtypes. All these factors explains why investigations into factors affecting PD subtypes are limited.

6.4. Risk and protective factors for PD progression

Few studies have dealt with the potential effects of risk factors for the onset of PD on the progression of the disease itself. Although the findings are often contrasting, evidence suggests that coffee may slow the progression of PD whereas cardiovascular comorbidities may accelerate it. A major drawback of this type of study is the lack of valid, reliable and easy-to-assess clinical or biological markers of disease progression.

Some of the modifiable risk factors for which the longitudinal studies considered here provided the most robust evidence may be targeted in strategic preventive interventions aimed at reducing the risk of PD and/or slowing its progression (Defazio, 2011). In this regard, physical activity and moderate doses of caffeine are good candidates for the primary prevention of PD, while the use of β2-adrenoceptor agonists in synucleinopathies is based on a rationale that merits further investigation. The observation that increased levels of serum urate concentrations may exert a protective effect on PD development and progression has led to interventional clinical trials with the urate precursor inosine. In 2014, Schwarzschild et al., 2014 demonstrated that inosine was safe, tolerable, and effective in raising serum and cerebrospinal fluid urate levels in early PD. An ongoing clinical trial is testing the PD modifying potential of inosine in a large population of untreated patients (SURE III- PPD) (Elkouzi, 2019).

7. Conclusions

In the present paper we reviewed all the possible risk/protective factors for PD examining only prospective cohort studies. By using a new method of stratification of the possible risk/protective factors, we found that 11 factors may affect the risk of developing PD. For the first time, we also reviewed the current literature on risk/protective factors for PD subtypes and PD progression. We observed that the contribution of modifiable risk/protective factors to the clinical subtype and progression in PD is still largely unexplored. Further research on the effect of modifiable risk factors on disease progression would also help to determine whether these factors may represent effective targets for preventive interventions aimed at reducing the risk of PD. Our review also highlights the importance of sufficient power in longitudinal studies that assess factors for which evidence is inconclusive. Another gap that needs to be filled is the limited amount of information available on the relative strength of risk factors for PD: the simultaneous assessment of a wide number of potential protective or risk factors would help to fill this gap.

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Declaration of Competing Interest

All authors reported no conflict of interest.

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Appendix A. Supplementary data

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