Review

Prevalence of Parkinson Disease in Italy: a systematic review and meta-analysis

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Abstract. Introduction: Parkinson's disease (PD) is a common disease of unknown etiology. Even though accurate information on the epidemiology of PD is critical for defining appropriate health policies, epidemiological data on Parkinson's disease (PD) in Italy are often defined as scant or conflicting. Our study attempted to provide an overview on the prevalence of (PD) by means of a systematic review and metanalysis of existing data. Material and methods: We searched into two different databases (PubMed and EMBASE), focusing on studies reporting the prevalence of PD in Italy. Data were extracted using a standardized assessment form, and results of such analyses were systematically reported, summarized and compared. Results: A total of 16 studies were eventually included in the analyses, with a prevalence rate of 193.7/100,000. Available reports were heterogeneous both in design and in eventual figures, and also prevalence estimates were affected by substantial heterogeneity. Interestingly, prevalence rates ranged from 37.8/100,000 inhabitants in subjects aged 0 to 64 years, to 578.7 in age group 65 to 75 years, and 1235.7 in age group 75 years or older. PD was significantly associated with male sex, but only in older age groups (i.e. Odds Ratio, OR 1.37 95%CI 1.22-1.53, and OR 1.31, 95%CI 1.21-1.42 for age groups 65-74 years and 75 years or more, respectively). Discussion and conclusion: While the observed variations in prevalence rates may result from environmental or genetic factors, differences in methodologies for case ascertainment and diagnostic criteria may have significantly affected our estimates. As a consequence, the comparability of existing studies is limited.

Keywords: Parkinson's disease; Parkinsonism; prevalence; epidemiology; occurrence;

Introduction

Parkinson disease (PD) is a common progressive, neurodegenerative disorder in adult population (1), characterized by four cardinal motor signs (i.e. tremor, rigidity, bradykinesia/akinesia and postural instability) and non-motor symptoms such as depression/psychosis, and autonomic and gastrointestinal dysfunction (1–3), that considerably impair the quality of life of PD patients.

Despite the main pathological feature of PD is well defined (i.e. the loss of dopaminergic neurons), current understanding of its etiology remains incomplete. In facts, while genetic factors have been strongly identified within PD pathogenesis (e.g. SNCA A53T gene mutation; upregulation of alpha-synuclein; impairment of the mitochondrial function following mutations of genes PINK-1 and Parkin), evidence regarding environmental (i.e. residential exposure to certain pesticides, rural living, but also exposure to waste incinerators fumes and industrial pollutants), and occupational factors (i.e. manganese, trichloroethylene, carbon monoxide) remains disputed (2,4-8). In facts, discerning between PD (or, more appropriately, Primary Parkinsonism) and secondary parkinsonisms is still difficult (1-3,9).

Even though imaging techniques can assist an appropriate assessment of suspected cases, PD diagnosis remains essentially based on clinical assessment (1,2,9,10). As a consequence, epidemiological data are often strikingly heterogeneous: even though variability in the occurrence of PD is usually explained by means of environmental and genetic factors, it is reasonable that other differences, such as methodological diversity and reliability of primary diagnosis, may play a significant role, complicating comparisons across studies (2,3,10–12). For example, a previous study summarizing European prevalence rates identified figures ranging from 65.6/100,000 in Sardinia, to 12,500/100,000 for German institutionalized patients (3). That said, available figures suggest that the prevalence of PD in high-income countries may be generally estimated at 0.3% for the entire population, and about 1% in people over 60 years of age (1,2,10,12).

Interestingly enough, previous studies suggested that prevalence data for Italian population may be even

more heterogenous, possibly reflecting both methodological and demographic issues (1–3). As a consequence, also estimates for the PD burden are particularly conflicting, ranging from 230,000 (following the public statement of the Italian Ministry of Health) to 600,000 cases. While the longevity of the Italian population steadily increases, the high financial burden associated with the chronic management of PD urges for accurate information about its actual epidemiology.

This survey will therefore provide an overview of the prevalence of PD in Italy, focusing on the methodologies used in the reported studies.

Materials and Methods

This systematic review has been conducted following the PRISMA (Prepared Items for Systematic Reviews and Meta-Analysis) guidelines (13). We searched into two different databases (PubMed and EMBASE) for relevant studies to 31/12/2019, without any chronological restriction. The search strategy was a combination of the following keywords (free text and Medical Subject Heading [MeSH] terms): (*«Parkinson»* OR *«Parkinson's disease»* OR *«Parkinsonism»*) AND (*«Italy»* OR *«Italian»*) AND (*«epidemiology»* OR *«prevalence»* OR *«frequency»*) (Figure 1). Records were handled using a references management software (Mendeley Desktop Version 1.19.5, Mendeley Ltd 2019), and duplicates were removed.

Articles eligible for review were original research publications available online or through inter-library loan. Articles had to be written in Italian, English, German, French or Spanish, the languages spoken by the investigators. Studies included were national and international reports, case studies, cohort studies, case-control studies and cross-sectional studies. Only article reporting diagnostic criteria for PD cases, the number of prevalent cases, or crude prevalence rates, were eligible for the full review. Articles were excluded if: (1) full text was not available; (2) articles were written in a language not understood by reviewers; (3) reports lacked significant timeframe (i.e. the prevalence year); (4) reports lacked geographical settings; (5) diagnostic criteria hinted towards a parkinsonism rather than PD.



Figure 1. PRISMA flow diagram including keywords employed for the inquiry (i.e. «Parkinson» OR «Parkinson's disease» OR «Parkinsonism») AND («Italy» OR «Italian») AND («epidemiology» OR «prevalence» OR «frequency»)).

Two independent reviewers (GG and LV) reviewed titles, abstracts, and articles. Titles were screened for relevance to the subject. Any articles reporting original studies, which did not meet one or more of the exclusion criteria, were retained for fulltext review. The investigators independently read fulltext versions of eligible articles. Disagreements were resolved by consensus between the two reviewers; where they did not reach consensus, input from a third investigator (MR) was obtained. Further studies were retrieved from reference lists of relevant articles and consultation with experts in the field. Data abstracted included:

- Settings of the study: prevalence year, Italian region, level of assessment (i.e. community, province, region);
- (2) Source of information (i.e. patient records, either institutional or maintained by general practitioners or neurologists; door-to-door interviews; institutional databases);
- (3) Screening procedures, including: clinical assessment of patients or patient records; diagnostic questionnaires; diagnosis-related

groups compatible (DRG) with PD diagnosis from institutional databases; previous prescriptions of antiparkinsonian drug(s).

- (4) Reported diagnostic criteria;
- (5) Total number of prevalent PD cases, in total, by gender (M/F), and by reported age groups;
- (6) Number of reference population, both in general of by gender and age groups.

We first performed a descriptive analysis to report the characteristics of the included studies. Crude PD prevalence figures were initially calculated: if a study did not include raw data, either as number of prevalent cases, or referent population (either in general or by age groups), such figures were either reverse-calculated from available data, or obtained from the Italian National Institute of Statistics (ISTAT) site DEMO (http://demo.istat.it/). When two or more studies reported about a shared population (e.g. a study included community level data, or provincial data, that were then included a in regional study), available local-area data were removed from the larger study in order to avoid duplication of estimates. DEMO includes official Italian demographic data for the timeframe 1974 – 2019, at various geographical levels (i.e. national, regional, provincial, local communities). Pooled prevalence (prevalent cases/100,000 inhabitants) estimates were then calculated by means of a random effect model (in order to cope with the presumptive heterogeneity in study design), in general, and by age groups (i.e. 0-64 years; 65-74 years, ≥75 years) for all studies that allowed such stratification. Estimates of the association of PD diagnosis with male sex were similarly assessed as Odds Ratios (OR) with their correspondent 95% Confidence Intervals (95%CI).

 I^2 statistic was then calculated to quantify the amount of inconsistency between included studies; it estimates the percentage of total variation across studies that is due to heterogeneity rather than chance. I^2 values ranging from 0 to 25% were considered to represent low heterogeneity, from 26% to 50% as moderate heterogeneity and above 50% as substantial heterogeneity, being pooled using a fixed-effects model because of the reduced number of samples eventually included.

To investigate publication bias, contour-enhanced funnel plots were initially generated: publication bias was evaluated by testing the null hypothesis that publication bias does not exist by means of the regression test for funnel plot asymmetry. The null hypothesis was rejected if the p-value is less than 0.10.

All calculations were performed in R (version 3.6.1; R Core Team, 2017. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/) and RStudio (version 1.2.5019) software by means of *meta* package (version 4.9-9), functions *metaprop* for pooling of HD prevalence, and *metabin* for comparison of prevalence data by gender. The meta package is an open-source add-on for conducting meta-analyses.

Results

Initially, 2973 entries were identified: as 2045 of them were duplicated across the sources, a total of 928 entries were initially screened. After applying the inclusion and exclusion criteria (**Figure 1**), 47 articles were assessed for eligility, with the subsequent removal of 13 articles not reporting actual prevalence data, 3 articles not reporting the settings of the study (or reporting it in unclear geographical/chronological terms), 1 article exhibiting unclear case definition. Similarly, 7 articles that eventually duplicated results of similar researches, and 7 further reports including data on parkinsonism rather than on PD were excluded from the analyses.

Eventually, 16 paper published between 1978 and 2019 fulfilled inclusion and exclusion criteria, being analyses and summarized (14–29) (**Table 1**).

Overall, 4 reports included data retrieved at regional level (25.0%) (18,20–22), 6 studies reported figures at provincial level (37.5%) (14–16,19,27,29), 5 studies with 6 estimates at community level (31.3%) (23–26,28), with 1 estimate at national level (5.9%) (Figure 2) (17). The pooled population included a total of 28,445 cases for a total sample size of 9,358,777 people: compared to the demographic estimates for 2019, reference areas would include around 24.1% of total Italian residents. Unfortunately, accurate description of the prevalent PD cases by age groups were retrieved only for 10 studies (11 estimates), being included in further analyses.



Figure 2. Geographic locations of studies performed on the prevalence of Parkinson's disease in Italy (1979 – 2019), and included in the meta-analysis. Deep gray = data retrieved at provincial and/or regional level, by sex and age groups; light grey = data retrieved at provincial and/or regional level.

Table 1. Prevalence estimates of Primary Parkinson's Disease (PD) in Italy. Notes: DRG = diagnosis-related groups; GP = General practitioner; APD = antiparkinsonian drug.

Assessed Cases Crude rate	Population (/100,000 inhabitants)	397,891 302 75.9		273,421 182 66.6	273,421 182 66.6 1,473,800 967 65.5	273,421 182 66.6 1,473,800 967 65.5 22,322 34 152.3	273,421 182 66.6 1,473,800 967 65.5 22,322 34 152.3 24,396 63 280.7	273,421 182 66.6 1,473,800 967 65.5 22,322 34 152.3 24,396 63 280.7 19,900 29 145.7	273,421 182 66.6 1,473,800 967 65.5 1,473,800 967 65.5 22,322 34 152.3 22,322 34 152.3 24,396 63 280.7 19,900 29 145.7 8,477 16 188.7
sria Populatio		signs or more 397,891	_	signs or more 273,421	signs or more 273,421	signs or more 273,421 isigns or more 1,473,800 isigns or more 22,322	signs or more 273,421 signs or more 1,473,800 signs or more 22,322 signs or 24,396 ents. one sign tore in treated ents. this on of all his on of all treates treits.	signs or more 273,421 vigns or more 1,473,800 vigns or more 22,322 signs or 24,396 ents, one sign ore in treated ents. twison of all twison of all twison of all twison of all twison of all twison fall this or 19,900 ents.	signs or more 273,421 signs or more 1,473,800 signs or more 22,322 signs or more 24,396 in untreated ents; one sign treated ents. trossible causes intreated ents. signs or 19,900 e in untreated ents. signs or ents. signs or ents. ents.
D criteria Two signs or more	Two signs or more		Two signs or more	-	Two signs or more	Two signs or more Two signs or more	Two signs or more Two signs or more Two signs or more in untreated patients, one sign or more in treated patients. Exclusion of all other possible cause. of parkinsonism.	Two signs or more Two signs or more Two signs or more Two signs or more in untreated patients, one sign patients. Exclusion of all other possible cause. of parkinsonism. Two signs or patients.	Two signs or more Two signs or more Two signs or more Two signs or patients, one sign or more in untreated patients. Exclusion of all other possible cause. of parkinsonism. Two signs or patients. History of signs/ symptoms in treate/ patients.
$ \begin{array}{c c} 3 & Anti-PD \\ \hline drugs \\ - & Ta \\ - & Ta \\ \end{array} $	- Tu	- Tw		- <i>Tu</i>		-	$- \frac{17u}{pau}$	$\begin{array}{c c} - & & 1^{T_{u}} \\ \hline & & & & \\ \hline & & & & \\ & & & & \\ & & & &$	$\begin{array}{c c} - & Iu \\ \hline & Iu \\ - & mo \\ pau \\ $
iire DRG		1		I	I		1	ı ı	ı
Questionna		I	I	T	I		YES	YES -	YES -
Clinical		YES	YES	YES	YES		YES	YES	YES
		Patient record	Patient record	Patient record	Patient record		Door-to-Door	Door-to-Door Patient record (GPs)	Door-to-Door Patient record (GPs)
alence	years	1971	1972	1972	1986		1987	1987	1987 1988 1989
		Province (Sassari)	Province (Nuoro)	Region	Community	(San Marmo)	(San Marmo) Community (Térrasini; Santa Téresa di Riva, Riposto).	(San Marmo) Community (Terrasini, Santa Teresa di Riva, Riposto). Riva, Riposto). Community (Arcisate)	(San Marmo) Community (Terrasini, Santa Teresa di Riva, Riposto). Riva, Riposto). (Arcisate) (Arcisate) Community (San Giovanni Rotondo)
		Sardinia	Sardinia	Sardinia	Emilia – Romagna		Sicily	Sicily Lom-bardy	Sicily Lom- bardy Apulia
		Rosati et al. 1978 (14)	Rosati et al. 1979 (15)	Rosati et al. 1980 (22)	D'Alessandro et al. 1986	(23)	(23) Morgante et al. 1992 (24)	(23) Morgante et al. 1992 (24) Beghi et al. 1994 (a) (25)	(23) Morgante et al. 1992 (24) Beghi et al. 1994 (a) (25) 1994 (b) (25)

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Table

231.6	104.2	346.3	379.8	238.7	335.6
682	14	2425	606	2204	10,632
294,424	13,431	700,328	239,325	923,356	3,167,777
Two signs or more in untreated patients, one sign or more in treated patients. Exclusion of all other possible causes of parkinsonism.	Previous diagnosis of PD or Parkin- sonism.	Integration of phar- macological records and medical records of the local Health Unit.	Integration of phar- macological records and medical records of the local Health Unit.	Integration of phar- macological records and medical records of the referring GPs. Exclusion of patients with less than 1 year of follow-up.	At least one bospital discharge diagnosis of PD, OR a specific exemption for PD, OR a minimum of two separate pre- scription for at least one APD.
YES	YES	YES	YES	YES	YES
YES	YES	YES	YES	YES	YES
1	YES	I	1	1	1
YES	YES	1	1	YES	1
Institutional database (mul- tiple)	Institutional database (mul- tiple)	Institutional database (mul- tiple)	Institutional database (mul- tiple)	Institutional database (mul- tiple)	Institutional database (mul- tiple)
2001	2001	2008	2011	2013	2010
Province (L'Aquila)	Community (Aeolian Islands)	Province (Bergamo)	Province (<i>Trieste</i>)		Region
Abruzzo	Sicily	Lom- bardy	Friuli Venezia Giulia	Nation- wide	Tuscany
Totaro et al. 2005 (27)	Morgante et al. 2008 (28)	Zucchi et al. 2011 (29)	Tominz et al. 2015 (16)	Pupillo et al. 2016 (17)	Baldacci et al. 2016 (18)

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214.3	387.7	617.2
1149	4735	5500
536,237	1,221,218	891,181
Two signs or more reported from at least 3 years without features of a possible alternative diag- nosis; documented response to APD.	At least one bospital discharge diagnosis of PD, OR a specific exemption for PD, OR home care for PD, OR nursing home admission with a diagnosis of PD, OR a mini- mum of 3 separate prescription for at least one APD during at least 6 consecutive months.	At least one hospital discharge diagnosis of PD, OR a specific exemption for PD, OR a minimum of 3 separate prescription for at least one APD during at least 6 consecutive months.
YES	YES	YES
YES	YES	YES
1	1	1
YES	1	I
Institutional database (mul- tiple)	Institutional database (mul- tiple)	Institutional database (mul- tiple)
2014	2016	2016
Province (<i>Trento</i>)	Region	Region
Trentino -Sud Tyrol	Friuli Venezia Giulia	Umbria
Malaguti et al. 2016 (19)	Valent et al. 2018 (20)	Eusebi et al. 2019 (21)

Focusing on the diagnostic assessment, while nearly all earlier reports retrieved PD cases by means of the analysis of patient records (14,15,22,23,25), since 1998 the majority of them were based on the retrospective analysis of institutional databases (16– 21,26–29), with only one study identifying PD cases by means of door-to-door analysis (24). Even more recent reports were somewhat heterogenous in terms of diagnostic criteria, with an increasing relevance for reports based on the analysis of prescription history rather than on clinical criteria.

Pooled estimates for PD prevalence are reported in Figure 3, being initially presented by subgroups represented by the three conventional Italian macroregions (i.e. North, Center, South), plus Sardinia. Briefly, individual estimates ranged from 60.2/100,000 inhabitants (95%CI 59.5 to 75.0), in the regional study of Rosati et al. on Sardinian residents (after the removal of data about the otherwise reported provinces of Nuoro and Sassari) (22), to 617.2/100,000 in the regional study of Eusebi et al. on the Central Italian Region of Umbria (21), with a relevant heterogeneity across the studies $(I^2 = 100\%)$. In facts, pooled prevalence estimates of 193.7/100,000 (95%CI 141.8 to 264.6) included the very low rates of Sardinia (66.8/100,000), very high rates from Central Italy (455.1/100,000), and intermediate figures for Northern (241.3/100,000) and Southern (197.2/100,000) Italy.

When prevalence rates were assessed by age groups, an increasing trend was clearly evident, with a pooled prevalence rate of 37.8/100,000 (95%CI 25.2 to 56.5) in subjects aged 0 to 64 years (**Figure 4**), that increased to 578.7/100,000 (95%CI 373.5 to 895.5) in the age group 65 to 74 years (**Figure 5**), and to 1235.7 (806.9 to 1888.1) in age group 75 years or more (**Figure 6**). Still, it should be stressed that heterogeneity was substantial, with I² values ranging from 99% to 100% in the three estimates.

Association of PD with male sex was then assessed, in general and by age group, and results are reported in **Figure 7**. In summary, while overall estimates testified a substantial association of PD status with male sex was reported only in the study of Baldacci et al (OR 2.06, 95%CI 1.99 to 2.13)(18), in older age groups a stronger association was identified (pooled OR 1.37, 95%CI 1.22 to 1.53 and OR 1.31,

95%CI 1.21 to 1.42 for age 65 to 74 years and 75 years or more, respectively), with lower heterogeneity, i.e. I² 48% for age group 65 to 74, and 58% for age group 75 or more.

The presence of publication bias was then evaluated using funnel plots and regression test for funnel plot asymmetry. Each point in funnel plots represents a separate study and asymmetrical distribution indicates the presence of publication bias. First, studies' effect sizes were plotted against their standard errors: the visual evaluation of the funnel plot suggested the absence of a significant publication bias, as the graph appeared substantially symmetrical (**Figure 8**). Subjective evidence from the funnel plot was confirmed by the regression test (Z = -0.702, p-value = 0.483).

Discussion

This study attempted to summarize available prevalence studies on PD in Italy. In order to obtain the larger base of evidence available, we forcibly included studies of very heterogenous quality and design, published between 1978 and 2019. Obviously, such approach resulted in high heterogeneity across the retrieved studies. The resulting pooled prevalence estimate of 193.7/100,000 was substantially lower than that previously reported in the nationwide study of Pupillo et al., i.e. 238.7/100,000 (95%CI 228.8 to 248.9) (17), but somehow similar to other reports from Western Europe previously summarized by von Campenhausen et al. in 2005 (2,3,10). Similarly, when reporting prevalence rates by age groups with the Italian census of 2019, a cumulative disease burden of 175,972 prevalent cases was estimated, that is around 25% less than that usually acknowledged by the Italian Ministry of Health (i.e. 230,000 cases in 2017).

The heterogeneity of reported estimates may find several explanations. First at all, diagnostic criteria for PD and methodologies applied for case ascertain have radically changed over the years, with increasing role for studies based on inquiries of institutional databases (i.e. use of certain combinations anti-parkinsonian drugs in subjects with individual clinical stories compatible with a diagnosis of PD): even though such search strategy was found sufficiently accurate when

			Events per 100000		
Study	Number	Total	observations	Events	95%-CI
Area = 1. North					
D'Alessandro et al. 1986	34	22322		152.3	[105.5; 212.8]
Beghi et al. 1994 (a)	29	19900		145.7	[97.6; 209.2]
Chiò et al. 1998	104	61830		168.2	[137.5; 203.8]
Zucchi et al. 2009	2425	700328	*	346.3	[332.6; 360.3]
Tominz et al. 2015	909	239325	-#-	379.8	[355.6; 405.3]
Malaguti et al. 2016	1149	536237	*	214.3	[202.1; 227.0]
Valent et al. 2018**	3826	981893		389.7	[377.4; 402.2]
Random effects model		2561835		241.3	[178.2; 326.6]
Heterogeneity: $I^2 = 99\%$, τ^2	= 0.1576, p	< 0.01			
Area = 2. Center					
Baldacci et al. 2016	10632	3167777		335.6	[329.3; 342.1]
Eusebi et al. 2019	5500	891181	+	617.2	[601.0; 633.6]
Random effects model		4058958		455.1	[298.2; 694.0]
Heterogeneity: $I^2 = 100\%$, τ	² = 0.0935,	p < 0.01			
Area = 3. South					
Morgante et al. 1992	63	24496		257.2	[197.7; 328.9]
Beghi et al. 1994 (b)	16	8477		188.7	[107.9; 306.3]
Totaro et al. 2005	682	294424	+	231.6	[214.6; 249.7]
Morgante et al. 2008	14	13431	- <u>-</u>	104.2	[57.0; 174.8]
Random effects model		340828		197.2	[144.3; 269.4]
Heterogeneity: $I^2 = 78\%$, τ^2	= 0.0636, p	0 = 0.02			
Area = 4. Sardinia					
Rosati et al. 1978	302	397891		75.9	[67.6; 85.0]
Rosati et al. 1979	182	273421		66.6	[57.2; 77.0]
Rosati et al. 1980*	483	802488		60.2	[54.9; 65.8]
Random effects model		1473800	•	66.8	[59.5; 75.0]
Heterogeneity: $I^2 = 67\%$, τ^2	= 0.0069, p) = NA			
Area = 5. Nationwide					
Pupillo et al. 2016	2204	923356		238.7	[228.8; 248.9]
Random effects model		923356	*	238.7	[228.9; 248.9]
Heterogeneity: not applicabl	е				
Random effects model		9358777	~	193.7	[141.8; 264.6]
Heterogeneity: $I^2 = 100\%$, τ	² = 0.4189,	$\rho = 0$			
Residual heterogeneity: I ² =	99%, p = (D	100 200 300 400 500 600 Prevalence (/100,000 inhabitants)		

Figure 3. Forest plot of retrieved studies on the prevalence of Parkinson's Disease. Prevalence data are reported as cases/100,000 inhabitants with their correspondent 95% confidence intervals (95%-CI). Notes: (a) data on the community of Arcisate; (b) data on the community of San Giovanni Rotondo; * = after removal of cases and population reported from Rosati et al. 1978 and Rosati et al. 1979; ** = after removal of Tominz et al. 2015.



Figure 4. Forest plot of retrieved studies on the prevalence of Parkinson's Disease, in age group 0 to 64 years. Prevalence data are reported as cases/100,000 inhabitants with their correspondent 95% confidence intervals (95%-CI). Notes: (a) data on the community of Arcisate; (b) data on the community of San Giovanni Rotondo; * = after removal of Tominz et al. 2015.

a comparison with real-world data was available (18,20,21,29), subsequent estimates are often limitedly comparable with field studies.

Second, because of its tormented history, and following millennia of migratory influxes, the genetic background of the Italian peninsula is usually acknowledged as strikingly heterogenous (30,31). Even though PD is usually understood as a multifactorial disorder, the genetic background is indisputably a major player in its natural history (2,9,10), either decreasing or increasing individual susceptibility to behavioral, environmental, or even occupational risk factors. Not coincidentally, the lowest prevalence rates were identified in studies based in a very peculiar region as Sardinia (14,15,22), and also the study on the residents of Aeolian island reported low prevalence rates (28). Third, Italy is also heterogenous in terms of economic development: not only northern regions are usually characterized by a highly developed industrial sectors, but the very same industrial or agricultural activities may be performed in strikingly different settings, with consequent differences in occupational and/or residential exposures, and possible heterogeneity in the occurrence of PD in exposed people (32–36).

Our study identified a clear trend across age groups, with prevalence rates increasing more than ten times from 37.8/100,000 in subject aged less than 65 years, to 578.7/100,000 in subjects aged 65 to 74 years, eventually doubling in older groups (\geq 75 years). Such trend was not unexpected, as PD is also usually acknowledged as strikingly age-dependent (2,3,10,11,17), and our estimates were quite similar

			Eve	nts per 100000		
Study	Number	Total	0	bservations	Events	95%-CI
Area = 1. North			1			
Beghi et al. 1994 (a)	9	1484		-	606.5	[277.7; 1148.1]
Chiò et al. 1998	33	6738			489.8	[337.4; 687.1]
Tominz et al. 2015	207	32883	-		629.5	[546.9; 721.0]
Valent et al. 2018*	990	118550			835.1	[784.1; 888.5]
Random effects model		159655	0		661.1	[528.7; 826.5]
Heterogeneity: $I^2 = 81\%$, τ^2	= 0.0308, j	0 < 0.01				
Area = 2. Center						
Baldacci et al. 2015	4	1212 -			330.0	[90.0; 842.8]
Eusebi et al. 2019	970	102139		+	949.7	[891.1; 1011.1]
Random effects model		103351			686.1	[318.5; 1471.5]
Heterogeneity: $I^2 = 53\%$, τ^2	= 0,1445, j	0 < 0.01				
Area = 3. South						
Morgante et al. 1992	22	1830			1202.2	[754.9; 1814.5]
Beghi et al. 1994 (b)	8	572		*	1398.6	[605.7; 2737.1]
Morgante et al. 2008	185	36509	*		506.7	[436.5; 585.0]
Totaro et al. 2005	3493	422020			827.7	[800.6; 855.5]
Random effects model		460931	-	-	825.0	[561.1; 1211.5]
Heterogeneity: $I^2 = 94\%$, τ^2	= 0.1095. /	0 = 0.03				
Area = 4. Nationwide						
Pupillo et al. 2016	87	100837 🗆			86.3	[69.1; 106.4]
Random effects model		100837 •			86.3	[69.9; 106.4]
Heterogeneity: not applicat	le					
Random effects model		824774	-		578.7	[373.5; 895.5]
Heterogeneity: $I^2 = 99\%$, τ^2	= 0.5079, (0 < 0.01				
Residual heterogeneity: 12:	= 91%, p <	0.01	500 10	00 1500 2000 2	2500	
			Prevalence	//100 000 inhabitar	(atc)	

Figure 5. Forest plot of retrieved studies on the prevalence of Parkinson's Disease, in age group 65 to 74 years. Prevalence data are reported as cases/100,000 inhabitants with their correspondent 95% confidence intervals (95%-CI). Notes: (a) data on the community of Arcisate; (b) data on the community of San Giovanni Rotondo; * = after removal of Tominz et al. 2015.

to those reported by the European study from von Campenhausen et al (2,3,10).

On the contrary, the clear and significant association of male sex with PD diagnosis in older age groups (i.e. 65 to 74 years, and \geq 75 years), while not totally unexpected, is somewhat conflicting with more doubtful evidence usually reported by epidemiological studies (2,10). Several explanations of conflicting association between sex and PD have been suggested, including neuroprotective effects of estrogens, but all remains controversial (2). More precisely, an increasing number of original field studies and subsequent systematic reviews and meta-analyses suggest that PD (or more appropriately parkinsonisms) may be elicited or even caused by exposures to occupational or environmental toxicants (e.g. heavy metals, pesticides, etc.) (4,6,32,37), and such evidences can lead to two opposite interpretations. On the one hand, we can deduce the increasing prevalence of PD in older age subjects, and particularly of male sex, as a consequence of cumulative, life-time exposure to the aforementioned risk factors, that are usually more frequently associated with occupations and work tasks performed by personnel of male sex (32,38,39). On the other hand, similarly to other multifactorial, work-related disorders (e.g. musculoskeletal disorders) (40–43), higher prevalence rates would be precisely expected in younger age groups, as occupational/residential exposures would anticipate the eventual diagnosis in a favorable background. Similarly, it should be stressed that while some

			Ev	rents per 100000			
Study	Number	Total		observations		Events	95%-CI
Area = 1. North							
Beghi et al. 1994 (a)	19	1210				1570.2	[948.0; 2441.3]
Chiò et al. 1998	49	6095				803.9	[595.3; 1061.5]
Tominz et al. 2015	634	34941		-#-		1814.5	[1677.1; 1959.9]
Valent et al. 2018*	2346	127114		*		1845.6	[1772.3; 1921.1]
Random effects model		169360	-			1449.9	[1032.6; 2032.5]
Heterogeneity: $l^2 = 97\%$, τ^2	= 0.1065. /	0 < 0.01					
Area = 2. Center							
Baldacci et al. 2015	7	916	-			764.2	[307.8; 1568.2]
Eusebi et al. 2019	3991	118822			*	3358.8	[3257.1; 3462.8]
Random effects model		119738				1710.0	[598:5; 4850.3]
Heterogeneity: $I^2 = 88\%$, τ^2	= 0.5291, /	0 < 0.01					
Area = 3. South							
Morgante et al. 1992	32	1311				2440.9	[1675.4; 3428.4]
Beghi et al. 1994 (b)	6	646				928.8	[341.6; 2010.6]
Morgante et al. 2008	428	26572				1610.7	[1462.8; 1769.4]
Totaro et al. 2005	4942	453188				1090.5	[1060.5; 1121.2]
Random effects model		481717	-			1453.8	[1053.3; 2003.6]
Heterogeneity: $I^2 = 96\%$, τ^2	= 0.0850, /	0 < 0.01					
Area = 4. Nationwide							
Pupillo et al. 2016	379	164192				230.8	[208.2; 255.2]
Random effects model		164192 •				230.8	[208.7; 255.2]
Heterogeneity: not applicab	le						
Random effects model		935007	-		_	1235.7	[806.9; 1888.1]
Heterogeneity: I ² = 100%, a	² = 0.4979,	p = 0		1 1 1	1		
Residual heterogeneity: I ² :	= 95%, p <	0.01	500 1000	1500 2000 2500	3000		

Figure 6. Forest plot of retrieved studies on the prevalence of Parkinson's Disease, in age group 75 years or more. Prevalence data are reported as cases/100,000 inhabitants with their correspondent 95% confidence intervals (95%-CI). Notes: (a) data on the community of Arcisate; (b) data on the community of San Giovanni Rotondo; * = after removal of Tominz et al. 2015.

earlier reports hinted towards higher rates in regions characterized by either agricultural (e.g. Apulia compared to Lombardy) (25,44,45), or highly developed industrial background (e.g. provinces of Bergamo and Brescia) (29,32), not only the prevalence rates reported from highly developed agricultural areas such as the Autonomous Province of Trento were relatively low, with similar occurrence in males and females (19), but most of available studies reported about parkinsonism rather than on PD (25,29,32,44,45), being therefore excluded from our analyses, and also hinting to a similar but distinctive series of neurological disorders.

Despite their potential interest, both for public health and clinical professionals, our results should be cautiously interpreted, for several reasons. In first place, as the studies were quite heterogenous, we cannot rule out that new reports may significantly modify eventual estimates, particular if involving areas characterized by genetic and/or geographical specificities (e.g. Alpine regions; mountainous enclaves, etc.). Second, studies based on the retrospective analysis of institutional databases may have failed to ascertain the actual prevalence of PD, either as unable to retrieve all diagnosis, or incorporating secondary parkinsonisms rather than PD cases (16,18,20,21). Third, even for accurate estimates, an original diagnostic bias cannot be totally ruled out. In other words, as the diagnosis of PD remains largely clinical, and no screening procedures have been made available, only subjects complaining one or more of the cardinal symptoms,

1. All age			Males		Females				
groups.	Study	Events	Total	Events	Total	Odds Ratio	OR	95%-CI	Weight
8. ou por	Morgante et al. 1992	27	12159	36	12337	<u> </u>	0.76	[0.46; 1.25]	9.6%
	Beghi et al. 1994 (a)	9	9534	20	10366		0.49	[0.22; 1.07]	7.1%
	Beghi et al. 1994 (b)	8	4053	8	4424		1.09	[0.41; 2.91]	5.7%
	Chiò et al. 1998	55	29998	49	32292		1.21	[0.82; 1.78]	10.6%
	l otaro et al. 2005 Morganto et al. 2009	328	144406	354	153373		0.98	[0.85; 1.14]	12.2%
	Baldacci et al. 2015	9596	1502092	5188	1665685		2.06	[1.99: 2.13]	12.5%
	Valent et al. 2018	2270	589761	2465	628175		0.98	[0.93; 1.04]	12.5%
	Eusebi et al. 2019	2628	427662	2848	463519	÷	1.00	[0.95; 1.05]	12.5%
	Pupillo et al. 2016	306	456122	252	448371		1.19	[1.01; 1.41]	12.1%
	Random effects model	1	3183007		3425203		1.05	[0.77; 1.44]	100.0%
	Heterogeneity: I^2 = 99%, τ^2	= 0.2074, µ	0 < 0.01			0.5 1 2			
$2 \Lambda a 0 to 61$			Males		Females	0.0 1 2			
2. Age 0 to 04	Study	Events	Total	Events	Total	Odds Ratio	OR	95%-CI	Weight
years	-								-
	Morgante et al. 1992	5	10752	4	10603		1.23	[0.33; 4.59]	9.6%
	Beghi et al. 1994 (a)	1	8552	0	8654		- 3.04	[0.12; 74.54]	4.1%
	Beghi et al. 1994 (b) Chiò et al. 1998	1	3548	1	3/11		1.05	[0.07; 16.73] [0.73: 4.17]	4.9%
	Totaro et al. 2005	36	118437	33	116261	·	1.07	[0.67: 1.72]	12.5%
	Morgante et al. 2008	2	6295	1	5458		1.73	[0.16; 19.13]	5.9%
	Baldacci et al. 2015	5444	1131594	905	1160975		6.20	[5.78; 6.65]	13.1%
	Valent et al. 2018	306	456077	252	448371		1.19	[1.01; 1.41]	13.0%
	Eusebi et al. 2019	279	332375	236	337845		1.20	[1.01; 1.43]	13.0%
	Pupillo et al. 2016	48	325572	44	313892	1	1.05	[0.70; 1.58]	12.6%
	Random effects model	:	2417929		2430500		1.59	[0.73; 3.47]	100.0%
	Heterogeneity: $I^2 = 99\%$, τ^2	= 1.2117,	p < 0.01						
3. Age 65 to	Study	Events	Males Total	i Events	Females Total	Odds Ratio	OR	95%-CI	Weight
3. Age 65 to 74 years	Study	Events	Males Total	l Events	Females Total	Odds Ratio	OR	95%-CI	Weight
3. Age 65 to 74 years	Study Morgante et al. 1992	Events 9	Males Total 839	I Events 13	Females Total 991	Odds Ratio	OR 0.82	95%-Cl [0.35; 1.92]	Weight
3. Age 65 to 74 years	Study Morgante et al. 1992 Beghi et al. 1994 (a)	Events 9 3	Males Total 839 624	Events 13 6	Females Total 991 860	Odds Ratio	OR 0.82 0.69	95%-Cl [0.35; 1.92] [0.17; 2.76]	Weight 1.6% 0.6%
3. Age 65 to 74 years	Study Morgante et al. 1992 Beghi et al. 1994 (a) Beghi et al. 1994 (b)	Events 9 3 3	Males Total 839 624 251	13 6 5	Females Total 991 860 321	Odds Ratio	OR 0.82 0.69 0.76	95%-Cl [0.35; 1.92] [0.17; 2.76] [0.18; 3.23]	Weight 1.6% 0.6% 0.6%
3. Age 65 to 74 years	Study Morgante et al. 1992 Beghi et al. 1994 (a) Beghi et al. 1994 (b) Chiò et al. 1998	Events 9 3 3 19	Males Total 839 624 251 2857	13 6 5 14	Females Total 991 860 321 3881	Odds Ratio	OR 0.82 0.69 0.76 1.85	95%-Cl [0.35; 1.92] [0.17; 2.76] [0.18; 3.23] [0.93; 3.69]	Weight 1.6% 0.6% 0.6% 2.4%
3. Age 65 to 74 years	Study Morgante et al. 1992 Beghi et al. 1994 (a) Beghi et al. 1994 (b) Chiò et al. 1998 Totaro et al. 2005	Events 9 3 3 19 93	Males Total 839 624 251 2857 16041	13 6 5 14 92	Females Total 991 860 321 3881 20468	Odds Ratio	OR 0.82 0.69 0.76 1.85 1.29	95%-Cl [0.35; 1.92] [0.17; 2.76] [0.18; 3.23] [0.93; 3.69] [0.97; 1.72]	Weight 1.6% 0.6% 0.6% 2.4% 10.3%
3. Age 65 to 74 years	Study Morgante et al. 1992 Beghi et al. 1994 (a) Beghi et al. 1994 (b) Chiò et al. 1998 Totaro et al. 2005 Morgante et al. 2005	Events 9 3 3 19 93 2	Males Total 839 624 251 2857 16041 564	13 6 5 14 92 2	Females Total 991 860 321 3881 20468 648	Odds Ratio	OR 0.82 0.69 0.76 1.85 1.29 - 1.15	95%-Cl [0.35; 1.92] [0.17; 2.76] [0.18; 3.23] [0.93; 3.69] [0.97; 1.72] [0.16; 8.19]	Weight 1.6% 0.6% 2.4% 10.3% 0.3%
3. Age 65 to 74 years	Study Morgante et al. 1992 Beghi et al. 1994 (a) Beghi et al. 1994 (b) Chiò et al. 1998 Totaro et al. 2005 Morgante et al. 2015 Baldacci et al. 2019	Events 9 3 19 93 2 1811	Males Total 839 624 251 2857 16041 564 195775 71408	13 6 5 14 92 2 1682	Females Total 991 860 321 3881 20468 648 226245	Odds Ratio	OR 0.82 0.69 0.76 1.85 1.29 - 1.15 1.25	95%-Cl [0.35; 1.92] [0.17; 2.76] [0.18; 3.23] [0.93; 3.69] [0.97; 1.72] [0.16; 8.19] [1.17; 1.33] [1.17; 1.33]	Weight 1.6% 0.6% 2.4% 10.3% 0.3% 30.1% 24.9%
3. Age 65 to 74 years	Study Morgante et al. 1992 Beghi et al. 1994 (a) Beghi et al. 1994 (b) Chiò et al. 1998 Totaro et al. 2005 Morgante et al. 2008 Baldacci et al. 2015 Valent et al. 2018 Fusebi et al. 2019	Events 9 3 19 93 2 1811 680 567	Males Total 839 624 251 2857 16041 564 195775 71408 48335	13 6 5 14 92 2 1682 517 403	Females Total 991 860 321 3881 20468 648 226245 80025 53804	Odds Ratio	OR 0.82 0.69 0.76 1.85 1.29 - 1.15 1.25 1.48 1.57	95%-CI [0.35; 1.92] [0.17; 2.76] [0.18; 3.23] [0.93; 3.69] [0.97; 1.72] [0.16; 8.19] [1.17; 1.33] [1.32; 1.66] [1.38; 1.79]	Weight 1.6% 0.6% 2.4% 10.3% 0.3% 30.1% 24.9% 23.3%
3. Age 65 to 74 years	Study Morgante et al. 1992 Beghi et al. 1994 (a) Beghi et al. 1994 (b) Chió et al. 1998 Totaro et al. 2005 Morgante et al. 2008 Baldacci et al. 2018 Valent et al. 2019 Pupillo et al. 2016	Events 9 3 3 19 93 2 1811 680 567 47	Males Total 839 624 251 2857 16041 564 195775 71408 48335 50313	I Events 13 6 5 14 92 2 1682 517 403 40	Females Total 991 860 321 3881 20468 648 226245 80025 53804 50524	Odds Ratio	OR 0.82 0.69 0.76 1.85 1.29 - 1.15 1.25 1.48 1.57 1.18	95%-Cl [0.35; 1.92] [0.17; 2.76] [0.18; 3.23] [0.93; 3.69] [0.97; 1.72] [0.16; 8.19] [1.17; 1.33] [1.32; 1.66] [1.38; 1.79] [0.77; 1.80]	Weight 1.6% 0.6% 2.4% 10.3% 0.3% 30.1% 24.9% 23.3% 5.8%
3. Age 65 to 74 years	Study Morgante et al. 1992 Beghi et al. 1994 (a) Beghi et al. 1994 (b) Chiò et al. 1998 Totaro et al. 2005 Morgante et al. 2015 Valent et al. 2018 Eusebi et al. 2019 Pupillo et al. 2016	Events 9 3 3 19 93 2 1811 680 567 47	Males Total 839 624 251 2857 16041 564 195775 71408 48335 50313	13 6 5 14 92 2 1682 517 403 40	Females Total 991 860 321 3881 20468 648 226245 80025 53804 50524	Odds Ratio	0.82 0.69 0.76 1.85 1.29 - 1.15 1.25 1.48 1.57 1.18	95%-Cl [0.35; 1.92] [0.17; 2.76] [0.18; 3.23] [0.93; 3.69] [0.97; 1.72] [0.16; 8.19] [1.17; 1.33] [1.32; 1.66] [1.38; 1.79] [0.77; 1.80]	Weight 1.6% 0.6% 2.4% 10.3% 0.3% 30.1% 24.9% 23.3% 5.8%
3. Age 65 to 74 years	Study Morgante et al. 1992 Beghi et al. 1994 (a) Beghi et al. 1994 (b) Chiò et al. 1998 Totaro et al. 2005 Morgante et al. 2005 Baldacci et al. 2015 Valent et al. 2018 Eusebi et al. 2019 Pupilo et al. 2016 Random effects model Heterogeneiit: I ² = 48%	Events 9 3 19 93 2 1811 680 567 47 81	Males Total 839 624 251 2857 16041 564 195775 71408 48335 50313 387007	13 6 5 14 92 2 1682 517 403 40	Females Total 991 860 321 3881 20468 648 226245 80025 53804 50524 437767	Odds Ratio	0.82 0.69 0.76 1.85 1.29 - 1.15 1.25 1.48 1.57 1.18 1.37	95%-Cl [0.35; 1.92] [0.17; 2.76] [0.18; 3.23] [0.97; 1.72] [0.97; 1.72] [1.17; 1.33] [1.32; 1.66] [1.38; 1.79] [0.77; 1.80] [1.22; 1.53]	Weight 1.6% 0.6% 2.4% 10.3% 0.3% 30.1% 24.9% 23.3% 5.8% 100.0%
3. Age 65 to 74 years	Study Morgante et al. 1992 Beghi et al. 1994 (a) Beghi et al. 1994 (b) Chiò et al. 1998 Totaro et al. 2005 Morgante et al. 2008 Baldacci et al. 2018 Eusebi et al. 2019 Pupillo et al. 2019 Random effects mode Heterogeneity: I ² = 48%,	Events 9 3 19 93 2 1811 680 567 47 el $\pi^2 = 0.0096$	Males Total 839 624 251 2857 16041 564 195775 71408 48335 50313 387007 5, ρ = 0.04	13 6 5 14 92 2 1682 517 403 40	Females Total 991 860 321 3881 20468 648 226245 80025 53804 50524 437767	Odds Ratio	0.82 0.69 0.76 1.85 1.29 - 1.15 1.25 1.48 1.57 1.18 1.37	95%-Cl [0.35; 1.92] [0.17; 2.76] [0.18; 3.23] [0.93; 3.69] [0.97; 1.72] [0.16; 8.19] [1.17; 1.33] [1.32; 1.66] [1.38; 1.79] [0.77; 1.80] [1.22; 1.53]	Weight 1.6% 0.6% 2.4% 10.3% 0.3% 30.1% 24.9% 23.3% 5.8% 100.0%
3. Age 65 to 74 years 4. Age 75	Study Morgante et al. 1992 Beghi et al. 1994 (a) Beghi et al. 1994 (b) Chiò et al. 1998 Totaro et al. 2005 Morgante et al. 2008 Baldacci et al. 2018 Eusebi et al. 2019 Pupillo et al. 2019 Random effects mode Heterogeneity: I ² = 48%,	Events 9 3 19 93 2 1811 6800 567 47 181 $r^2 = 0.0096$	Males Total 839 624 251 2857 16041 564 195775 71408 48335 50313 387007 6, <i>p</i> = 0.04 Males	I Events 13 6 5 14 92 2 1682 517 403 40	Females Total 991 860 321 3881 20468 648 226245 80025 53804 50524 437767	Odds Ratio	OR 0.82 0.69 0.76 1.85 1.29 - 1.15 1.25 1.48 1.57 1.18 1.37	95%-Cl [0.35; 1.92] [0.17; 2.76] [0.18; 3.23] [0.93; 3.69] [0.97; 1.72] [0.16; 8.19] [1.17; 1.33] [1.32; 1.66] [1.38; 1.79] [0.77; 1.80] [1.22; 1.53]	Weight 1.6% 0.6% 2.4% 10.3% 0.3% 0.3% 30.1% 24.9% 23.3% 5.8% 100.0%
3. Age 65 to 74 years 4. Age 75 years or more	Study Morgante et al. 1992 Beghi et al. 1994 (a) Beghi et al. 1994 (b) Chiò et al. 1998 Totaro et al. 2005 Morgante et al. 2008 Baldacci et al. 2019 Valent et al. 2019 Pupillo et al. 2019 Huerogeneity: I ² = 48%,	Events 9 3 19 93 2 1811 680 567 47 el $\tau^2 = 0.0096$ Events	Males Total 839 624 2511 2857 16041 564 195775 71408 48335 50313 387007 5, <i>p</i> = 0.04 Males Total	I Events 13 6 5 14 92 2 1682 517 403 40 F Events	Females Total 991 860 321 3881 20468 648 226245 80025 53804 50524 437767 Gemales Total	Odds Ratio	OR 0.82 0.69 0.76 1.85 1.29 - 1.15 1.25 1.48 1.57 1.18 1.37 OR	95%-Cl [0.35; 1.92] [0.17; 2.76] [0.18; 3.23] [0.93; 3.69] [0.97; 1.72] [0.16; 8.19] [1.72; 1.66] [1.38; 1.79] [0.77; 1.80] [1.22; 1.53] 95%-Cl	Weight 1.6% 0.6% 2.4% 10.3% 30.1% 24.9% 23.3% 5.8% 100.0% Weight
3. Age 65 to 74 years 4. Age 75 years or more	Study Morgante et al. 1992 Beghi et al. 1994 (a) Beghi et al. 1994 (b) Chiò et al. 1998 Totaro et al. 2005 Morgante et al. 2008 Baldacci et al. 2018 Eusebi et al. 2019 Pupillo et al. 2019 Pupillo et al. 2016 Random effects mode Heterogeneity: $I^2 = 48\%$, Study Morgante et al. 1992	Events 9 3 19 93 2 1811 680 567 47 el $\tau^2 = 0.0096$ Events 13	Males Total 839 624 251 2857 16041 1564 48335 50313 387007 6, <i>p</i> = 0.04 Males Total 568	1 Events 13 6 5 14 92 2 2 1682 517 403 40 40 F Events	Females Total 991 860 321 3881 20468 648 226245 80025 53804 50524 437767 Females Total 743	Odds Ratio	OR 0.82 0.69 0.76 1.85 1.29 1.15 1.25 1.48 1.57 1.18 1.37 OR	95%-Cl [0.35; 1.92] [0.17; 2.76] [0.18; 3.23] [0.93; 3.69] [0.97; 1.72] [0.16; 8.19] [1.72; 1.66] [1.38; 1.79] [0.77; 1.80] [1.22; 1.53] 95%-Cl [0.44; 1.82]	Weight 1.6% 0.6% 2.4% 10.3% 0.3% 30.1% 24.9% 23.3% 5.8% 100.0% Weight 1.2%
3. Age 65 to 74 years 4. Age 75 years or more	Study Morgante et al. 1992 Beghi et al. 1994 (a) Beghi et al. 1994 (b) Chiò et al. 1998 Totaro et al. 2005 Morgante et al. 2018 Baldacci et al. 2018 Pupillo et al. 2019 Pupillo et al. 2019 Random effects mode Heterogeneity: $I^2 = 48\%$, Study Morgante et al. 1992 Beghi et al. 1994 (a)	Events 9 3 19 93 2 1811 680 567 47 el Events 13 5	Males Total 839 624 251 2857 16041 564 195775 71408 48335 50313 387007 6, <i>p</i> = 0.04 Males Total 568 358	1 Events 13 6 5 14 92 2 1682 517 403 40 40 F Events 19 14	Females Total 991 860 321 3881 20468 226245 80025 53804 50524 437767	Odds Ratio	OR 0.82 0.69 0.76 1.85 1.29 1.15 1.25 1.48 1.57 1.18 1.37 OR 0.89 0.85	95%-Cl [0.35; 1.92] [0.17; 2.76] [0.18; 3.23] [0.93; 3.69] [0.97; 1.72] [0.16; 8.19] [1.17; 1.33] [1.32; 1.66] [1.38; 1.79] [0.77; 1.80] [1.22; 1.53] 95%-Cl [0.044; 1.82] [0.30; 2.37]	Weight 1.6% 0.6% 2.4% 10.3% 0.3% 30.1% 24.9% 23.3% 5.8% 100.0% Weight 1.2% 0.6%
3. Age 65 to 74 years 4. Age 75 years or more	Study Morgante et al. 1992 Beghi et al. 1994 (a) Beghi et al. 1994 (b) Chiò et al. 1998 Totaro et al. 2005 Morgante et al. 2018 Baldacci et al. 2015 Valent et al. 2019 Pupillo et al. 2019 Random effects mode Heterogeneity: $I^2 = 48\%$, Study Morgante et al. 1992 Beghi et al. 1994 (a) Beghi et al. 1994 (b)	Events 9 3 19 93 2 1811 680 567 47 el Events Events 13 5 4	Males Total 839 624 251 2857 16041 195775 71408 48335 50313 387007 5, <i>p</i> = 0.04 Males Total 568 358 254	1 Events 13 6 5 14 92 2 1682 517 403 40 40 F Events	Females Total 991 860 321 3881 20468 648 226245 80025 53804 50524 437767 Females Total 743 852 392	Odds Ratio	OR 0.82 0.69 0.76 1.85 1.29 1.15 1.25 1.48 1.57 1.18 1.37 OR 0.89 0.85 0.85	95%-Cl [0.35; 1.92] [0.17; 2.76] [0.18; 3.23] [0.93; 3.69] [0.97; 1.72] [1.12; 1.33] [1.32; 1.66] [1.38; 1.79] [0.77; 1.80] [1.22; 1.53] 95%-Cl [0.44; 1.82] [0.30; 2.37] [0.57; 17.16]	Weight 1.6% 0.6% 2.4% 10.3% 0.3% 30.1% 24.9% 5.8% 100.0% Weight 1.2% 0.6% 0.2%
3. Age 65 to 74 years 4. Age 75 years or more	Study Morgante et al. 1992 Beghi et al. 1994 (a) Beghi et al. 1998 Totaro et al. 2005 Morgante et al. 2008 Baldacci et al. 2015 Valent et al. 2018 Eusebi et al. 2019 Pupillo et al. 2016 Random effects mode Heterogeneity: $I^2 = 48\%$, Study Morgante et al. 1992 Beghi et al. 1994 (a) Beghi et al. 1994 (b) Chio et al. 1998	Events 9 3 19 93 2 1811 680 567 47 el $\tau^2 = 0.0096$ Events 13 5 4 22	Males Total 839 624 251 2857 16041 564 195775 71408 48335 50313 387007 5, <i>p</i> = 0.04 Males Total 568 3588 254 254	I Events 13 6 5 14 92 2 1682 517 403 40 40 5 17 403 40 5 17 403 40 5 17 403 40 5 17 403 40 5 17 403 40 5 17 403 40 5 5 5 7 14 9 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	Females Total 991 860 321 3881 20468 648 226245 80025 53804 50524 437767 Total 743 852 392 3681	Odds Ratio	OR 0.82 0.69 0.76 1.85 1.25 1.48 1.57 1.18 1.37 OR 0.89 0.85 0.89 0.85 1.24 0.82 0.9 0.76 0.82 0.76 0.82 0.76 0.75	95%-Cl [0.35; 1.92] [0.17; 2.76] [0.18; 3.23] [0.97; 1.72] [0.16; 8.19] [1.17; 1.33] [1.32; 1.66] [1.38; 1.79] [0.77; 1.80] [1.22; 1.53] 95%-Cl [0.44; 1.82] [0.44; 1.82] [0.30; 2.37] 0.57; 17.16] [0.71; 2.19]	Weight 1.6% 0.6% 2.4% 10.3% 0.3% 30.1% 24.9% 5.8% 100.0% Weight 1.2% 0.6% 0.2% 1.9%
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Figure 7. Forest plot of retrieved studies on the prevalence of Parkinson Disease, in the whole study population (1), in age groups 0-64 year-old (2), 65-74 year-old (3), 75 year-old or more (4): association of cases with male gender are assessed as Odds Ratios (ORs) with their correspondent 95% confidence intervals (95%-CI). Notes: (a) data on the community of Arcisate; (b) data on the community of San Giovanni Rotondo.



Z-0.702 P 0.483

Figure 8. Contour-enhanced funnel plots of available studies on the Italian prevalence of Parkinson disease.

appropriately interacting with a physician deserving to him/her patient an appropriate suspicion index (i.e. the general practitioner, or a medical specialist, including neurologists, psychologists, psychiatrics, or even professionals of sleep medicine), had a significant probability to obtain the diagnosis of PD, being therefore incorporated in the estimates we retrieved and analyzed. In this regard, it is noteworthy that the only door-to-door study we were able to analyze (24), was characterized by relatively high prevalence estimates (i.e. 257.2/100,000), nearly the double of those reported by the same Authors in the Aeolian island ten years after the first survey (i.e. 104.2/100,000) (28). Even though the latter study may have been significantly influenced by the genetic background of the study population, the role of the study design should not be undermined.

Conclusions

In summary, we identified a pooled prevalence rate of PD in Italy of 193.7/100,000 inhabitants. Such figures are well below previous estimates, and hint toward a disease burden of around 175,972 prevalent cases, i.e. one quarter less than previously suspected and usually reported by the Italian Health Ministry. Interestingly, we found both a significant age-dependent trend, with higher rates in older groups, and a relatively strong association of PD with male sex, but only in older age groups. Despite its limits, on the one hand our study stresses the importance of promoting large, appropriately designed population studies in order to guarantee a better definition of the actual epidemiology of PD in Italy; on the other hand, it also highlights how retrospective studies based on institutional databases and deprived of an accurate analysis (either preventive of retrospective) of potential cases by well-trained professionals may elicit doubtful or even unreliable epidemiologic assessments.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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