Age-related selection bias in Parkinson's disease research: are we recruiting the right participants?

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Abstract

Objective: To describe, and explore heterogeneity in, age at onset/diagnosis in Parkinson's disease (PD) and compare mean age at onset/diagnosis in incidence studies with that in general PD research studies.

Methods:

We systematically reviewed studies of PD incidence. We meta-analysed mean age at onset/diagnosis and age-stratum-specific incidence rates. We compared age-specific incidence rates in screening studies in the elderly with whole-population studies. We collated mean ages at onset/diagnosis in clinical studies of PD in five journals July–December 2016.

Results:

In 17 studies reporting sufficient data to pool, mean age at onset/diagnosis was 69.6 years (95% CI 68.2–71.1), but heterogeneity was high (I^2=96%). In ten of these studies reporting age at diagnosis specifically, the pooled mean age at diagnosis was slightly higher (71.6 [95% CI 70.6–72.6]) with lower, but still high, heterogeneity (I^2=84%). In twelve whole-population studies reporting age-specific incidence rates, these peaked in age 70-79 (pooled incidence rate per 100,000=93.8 [95% CI 80.3–107.6]). Heterogeneity increased with each increase in age stratum (0% in youngest to 88% in oldest age stratum). Pooled age-specific incidence rates in five population-based screening studies of older age groups were several-fold higher than in whole-population studies. The mean of the reported mean ages at onset/diagnosis in recently published research studies was 60.8 (SD 5.6).

Conclusion:

The mean age of onset/diagnosis PD is about 70, although this may be an underestimate due to under-diagnosis in the elderly. Many published studies use age-unrepresentative subjects: the effect of this selection bias deserves further study.

Introduction

Accurate knowledge of the age-distribution and mean age at onset of Parkinson's disease (PD) is important for several reasons. Firstly, it is a fundamental aspect of the disease epidemiology. Secondly, knowing this and other aspects of the epidemiology of PD is useful for health care planning as populations age.[1] Thirdly, it is important to enable the evaluation of the generalisability of clinical research, as many disease outcomes vary by age.[2-4]

Many authoritative sources quote the mean age of onset (be it motor symptom onset or diagnosis) in PD to be about 60,[5, 6] and some have even quoted younger ages,[7] although one recent review quoted a median age of 65.[8] However data from many population-based studies demonstrate that the mean age of onset in PD is substantially older. This apparent underestimation of the age of onset in PD may be because unrepresentative patient samples were used (for example, research is often from specialist centres where younger patients are more likely to be seen),[9] or that opinion leaders tend to work in specialist clinics and see younger patients. The only reliable way to identify the true age distribution in a population of PD is by population-based incidence studies, studies which aim to identify all new cases in a defined population and time period.

In this paper we used meta-analysis of incidence studies in PD to (i) describe the age distribution of PD at disease inception (i.e. either symptom onset or diagnosis); (ii) to explore heterogeneity in age at inception in these studies; and (iii) compare the mean age of inception in incidence studies with the mean age at inception in general research studies in PD. We have not reviewed the incidence rate of PD as such because an up-to-date systematic review of incidence studies was recently published.[10]

Methods

Systematic review

We updated a systematic review of incidence studies we previously published in 2003.[11] We sought to include all studies of PD incidence: either studies of the whole population or studies restricted to particular age strata only if they used door-to-door screening methodologies for case ascertainment. We excluded studies published before 1990 (as the distinction between PD and atypical parkinsonism was less clear prior to this). We excluded studies which made no attempt to confirm diagnosis by expert review of case notes or in-person assessment. We excluded studies published only in abstract form, but not on basis of language. We searched electronic databases to identify potential studies (MEDLINE and Embase up to September 2017) and reviewed reference lists of relevant studies. The electronic searches are shown in Supplementary Appendix 1). References were de-duplicated in bibliographic software. Titles and abstracts of studies identified from the search strategy were reviewed by two authors, and the full text of potentially relevant articles was obtained. We identified 10 criteria to assess the methodological quality of the included studies, based on recommendations regarding incidence studies in PD[11] and previous criteria suggested for incidence/prevalence studies in general.[12] Methodological features, demographic characteristics, incidence rates, and ages at onset/diagnosis were extracted from each study by two authors independently, with disagreements resolved by discussion. Many studies reported age at onset without further clarification, which we have presumed to refer to age at motor symptom onset.

Some studies reported mean age at inception without reporting a measure of precision (i.e. no standard error, standard deviation or confidence interval). Where the number of cases in each age stratum were also presented we estimated the standard error of the mean by assuming each case had age on onset in the middle of the age stratum (and assumed age 85 in the 80+ stratum), assumptions which may result in slightly wider confidence intervals.

Meta-analysis of age at inception

We used Der Simonian and Laird random effects meta-analysis[13] to pool data on mean age at inception (i.e. at diagnosis or, where age at diagnosis not reported, age at onset) in studies of the incidence in the whole population. We performed sensitivity analyses of pooled age at diagnosis and at onset separately. Heterogeneity was measured using the I^2 statistic.[14] We performed univariable random-effects meta-regression by mid-year of recruitment to the studies to assess whether age at inception varied with time.

Meta-analysis of age-specific incidence rates

In order to unravel the heterogeneity of the age at inception, we next performed random effects meta-analysis of age-specific incidence rates in ten-year age-bands, restricted to studies published since 2000 to minimise heterogeneity in time. We also did this separately in population-screening studies restricted to older age groups. We used the Rothman/Greenland method for estimating confidence limits for the incidence rate.[15] As the confidence interval for a rate of zero is undefined, in age strata in individual studies where no cases were identified we arbitrarily used an upper limit of confidence of 100 cases per 100,000. We compared heterogeneity between different age strata and compared results between studies which used door-to-door screening with those which used other methodologies for case ascertainment. We used pooled age-specific incidence rates to plot a histogram illustrating the distribution of age at inception of PD in the European Standard Population 2013.[16]

We have followed the Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guidelines in this paper.[17]

Review of published studies

We reviewed all PD research papers published over a recent six-month period (July 2016 to December 2016) in three general neurology journals (*Brain, JNNP,* and *Neurology*) and two movement disorder journals (*Movement Disorders* and *Parkinsonism and Related Disorders*). We aimed to include all studies of PD patients in general, but excluded studies which were restricted to specific groups which may be influenced by age of onset. For example, we excluded studies restricted to specific age distributions, PD with specific features relating to age (e.g. PD with dementia – more common in older-onset disease), specific mutations, and interventional treatments for complex PD (more common in young-onset) but we did not exclude studies restricted by gender or disease stage. From each study we documented the mean age at either diagnosis or onset in the PD participants, if necessary calculated from the mean age at study entry and mean disease duration.

Results

Twenty-nine studies were identified which reported the incidence of PD in the whole population and six further studies reported incidence in older age groups based on door-to-door screening. Details of the search results are shown in Supplementary Figure 1. Characteristics of included studies and their references are in Supplementary Table and results of quality assessment in Supplementary Appendix 2.

Of the whole-population studies, 20 (69%) reported the mean age at inception (nine reported mean age at symptom onset only, nine mean age at disease diagnosis only, two reported both). In 17 studies a measure of precision for the mean age at inception was either reported or estimable (Figure 1). The pooled mean age at inception in these studies was 69.6 years (95% CI 68.2–71.1), but heterogeneity was high (I^2 96%). Restricting this meta-analysis to eight studies with a quality score greater than six did not substantially alter the mean age at inception (70.7 [95% CI 68.3–73.1]). A meta-analysis of the ten studies reporting age at diagnosis gave a higher pooled mean age (71.6 [95% CI 70.6–72.6], I^2 84%) than the meta-analysis of nine studies reporting mean age at symptom onset (pooled mean age 68.1 [95% CI 65.8–70.4], I^2 96%). There was no evidence from meta-regression that age at inception varied with time (p=0.11).

The forest plot of incidence rates by age stratum in twelve whole-population studies since 2000 is shown in Figure 2. Incidence rates increased steeply with increasing age until the eighth decade (pooled incidence rate per 100,000 in 70-79 stratum 93.7 [95% CI 79.9–107.6]) with a fall in the 80+ group (pooled incidence rate per 100,000 80.6 [95% CI 59.7–101.5]). However, confidence intervals for these two strata overlapped and four studies found the highest incidence rate in the oldest age group. There was also a clear rise in heterogeneity with increasing age, from 0% in the youngest age stratum to 86% in the oldest. A histogram of the age distribution based on the pooled incidence rates is shown in Supplementary Figure 2.

Six age-restricted population screening studies reported age-specific incidence rates. Five of these reported comparable age strata to meta-analyse and these are presented separately because of different age bands reported (Supplementary Figure 3). Figure 3 shows a comparison which shows that the pooled estimates for the incidence rates in age-limited screening studies are several times higher than in the whole population studies, although a direct comparison was not possible due to different age strata analysed in the two study types. Two older-age screening studies used similar methodologies in the same population over different time periods and reported very different incidence rates,[18, 19] although the reasons for this were unclear.

The results of the review of the mean age at inception in research articles are displayed in Table 1. Details of these articles, including exclusions, are provided in supplementary appendix 3. The mean of the reported mean ages at inception was 60.8 (SD 5.7) and the median mean age at inception was 60.4 (interquartile range 57.7–63.7). The median age at inception in the excluded studies was lower (50.9).

Discussion

We have demonstrated that the mean age of motor onset and diagnosis of PD are about 70 in population-based incidence studies but this may be an underestimate, given the much higher incidences found in the older-age screening studies. There is clear heterogeneity in both age at

inception and in incidence rates, with increasing heterogeneity in incidence rates with increasing age. We also found that the average mean age of inception in research studies in PD was about 60, demonstrating that research participants are generally unrepresentative of the population age distribution of PD. These results raise four questions with important implications.

Firstly, why does heterogeneity increase with increasing age? One likely explanation for this is variability in case ascertainment in the elderly who will often be frail or have co-morbidities. Such individuals are less likely to be referred to a specialist with suspected PD[9] and data from other diseases suggest that age-related factors may lead to delayed presentations.[20, 21] Older people may accept more symptoms or higher disability before presenting to primary care providers and/or seeking onward referral to specialists. Furthermore, symptoms and signs of PD may be misinterpreted as normal ageing because many symptoms are non-specific and mild parkinsonian-like signs are common in the elderly.[22, 23] Therefore older people with PD may be more difficult to identify in epidemiological studies than younger people and require more intensive case finding strategies to identify them.

Another possible explanation of greater heterogeneity in the elderly is increased difficulty achieving accurate diagnosis in the elderly. Our personal experience is that formal diagnostic criteria are less useful in the elderly because exclusions from the UK PD Society Brain Bank criteria[24] such as a Babinski sign or early severe autonomic involvement are more common in this age group and the supportive criterion of excellent treatment response is less frequent, although we are unaware of published objective data to confirm this. In any case, different thresholds for diagnosis of PD in the elderly across different studies may contribute heterogeneity. These sources of heterogeneity are more likely to lead to underdiagnosing than over-diagnosing PD in the elderly and may cause under-estimation of the age at inception in PD.

Secondly, why are incidence rates in whole-population studies lower than in studies which screened small elderly populations? Each screening-based study in older adults was small and estimated incidence rates with wide confidence intervals. Yet the lower limits of confidence for the stratum-specific incidence rates in these studies are still higher than the upper limits in the whole population studies. It is possible that these studies used inadequate methods to screen out pre-existing cases at the initial population screens. But given that many of those diagnosed with PD in these studies were reviewed by a neurologist, it seems unlikely that many previously-diagnosed cases would have been included in incidence rates. Non-participation in the screening phase of these studies (18 to 32%) may have introduced bias, but even if none of those had PD, the incidence rates would still be higher than in many whole-population studies. As previously discussed, difficulties with diagnostic accuracy may be relevant (i.e. overdiagnosis of PD due to over-interpretation of mild signs in the elderly) but there were broadly-consistent incidence rates across these studies and some of the studies used formal diagnostic criteria. Overdiagnosis in the elderly could be minimised by follow-up to see whether they progress like PD, by more post-mortem confirmation and by the use of FP-CIT SPECT imaging.

Nevertheless, it seems unlikely that such methodological considerations explain such a dramatic difference in incidence rates between the study types. We therefore suggest that a large proportion of PD may remain undiagnosed in the elderly without screening, perhaps being mistaken for normal

ageing in some cases, or perhaps because more die from co-morbid disease before the parkinsonism becomes severe enough to present to medical attention. Further evidence for this comes from prevalence studies with population screening in which many cases have not been previously diagnosed (a pooled analysis of community surveys found 24% of PD subjects were previously undiagnosed).[25] Further investigation of the barriers to diagnosis in the elderly and the benefits of increased identification and treatment of this group is needed.

Thirdly, is the drop-off in the trend of rising incidence seen in the oldest real or spurious? Although the overall pooled incidence rate in those aged 80 and over was slightly less than the rate in those aged 70-79, the confidence intervals overlap widely. In several studies in this review, the incidence rate continued to rise in the oldest old. One study found that incidence rates in the oldest declined if strict diagnostic criteria were applied, were stable with intermediate criteria, but rose with broad diagnostic criteria were used.[26] This may relate to greater difficulties distinguishing PD from other disorders in the elderly as discussed above. However, we cannot rule out the possibility that incidence rates do fall in the oldest old and more pathological studies in the elderly are required to clarify this.

Fourthly, what are the implications of the under-representation of the elderly in most research studies? There is little doubt that many published studies of PD use relatively-younger-onset patients. This has previously been highlighted regarding clinical trials,[27, 28] and the implications of under-representing older people in trials are clear: treatment efficacy and safety may vary by age making it difficult to assess the benefits and disadvantages of treatment in the elderly. Aetiological and prognostic research may also be substantially biased if younger-onset samples are used. Genetic and environmental causes or risk factors are likely to vary with age and many outcomes are strongly associated with age.[2-4] The effect of this selection bias on studies of factors which influence prognosis is less clear; it is conceivable that the importance of prognostic factors varies by age, but we are not aware of studies which have investigated such an interaction. Studies of disease mechanisms in PD may be less affected by such selection biases, but gene-related mechanisms of neurodegeneration may have more impact in younger patients and the interactions between PD pathology, normal ageing, and co-morbid neurodegenerative pathology may be more easily investigated in the elderly.

This study has several strengths: we have systematically reviewed incidence studies, the only study type which provides unbiased data on the age at inception. We have also considered the effects of heterogeneity on the results. There are nevertheless some limitations. Fundamentally, defining PD onset is difficult as non-motor symptoms often precede motor onset by many years[29] and recall of motor onset may be inaccurate. Additionally, individual studies had varying quality and variable case-finding intensity, and we did not assess the effect of this on study heterogeneity, because measuring study quality objectively is difficult. The included studies were predominantly from developed countries, limiting generalisability to other countries, but age-stratum-specific incidence-rates can easily be applied to different age structures. Our separate pooled estimates of age at onset and age at diagnosis must be interpreted with caution because few studies reported both and there was high heterogeneity between studies, but age at onset was lower than age at diagnosis, as expected. The review of the age at inception in published research studies was limited to a small

number of journals over six consecutive months, but we believe this is representative of recent research in PD.

What should be done to solve the problem of under-representativeness of research in PD? While it is possible to recruit maximally-representative samples for research by recruiting as many incident or prevalent cases as possible from the population, this is often unrealistic as it is time-consuming, resource-intensive, and particular research procedures may be unsuitable for many frail, elderly, or cognitively-impaired subjects. Nevertheless, we believe that there is a strong argument that studies of prognosis/outcomes in PD should be derived from population-representative cohorts, ideally long-term follow-up of incident cohorts: high-quality research should use the best methodology to answer the research question.[30, 31] Furthermore, we suggest the following recommendations for all studies of PD: (i) researchers should attempt to recruit age-representative patient samples for studies where possible; (ii) authors should report the mean age of onset/diagnosis; (iii) authors should discuss potential implications of age-unrepresentativeness in terms of bias and external validity; and (iv) reviewers and editors should consider the impact of this issue when reviewing and publishing manuscripts.

In conclusion, PD is predominantly a disease of the elderly with a mean age of onset/diagnosis PD about 70. The true age at inception may be higher than this due to under-diagnosis in the elderly. Many published studies use age-unrepresentative subjects and the effect of this selection bias deserves further study. These issues deserve wider awareness from researchers, authors, reviewers, editors, and policy makers. We lastly propose that mean age at diagnosis is a simple and quick way to assess the representativeness of the patient sample in a research study.

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Rachel Henery, collection of data, analysis and interpretation of data, revision of manuscript for intellectual content
Paul C Nwajiugo, collection of data, analysis and interpretation of data, revision of manuscript for intellectual content
Nicholas W Scott, collection of data, analysis and interpretation of data, revision of manuscript for intellectual content
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Competing interests
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Figure Captions

Figure 1
Random-effects meta-analysis of mean age at either onset or diagnosis in 17 studies of the incidence of Parkinson's disease.

Figure 2
Random-effects meta-analysis of incidence rates in 10-year age strata in 12 whole-population incidence studies in Parkinson's disease.

Figure 3
Pooled summary estimates of incidence rates from random-effects meta-analyses comparing whole population incidence studies (blue crosses) and in screening studies restricted to older age groups (red circles).

Supplementary Figure 1
Flowchart of included studies.

Supplementary Figure 2
Histogram of frequency of the age of inception of Parkinson's disease derived from age-stratum-specific incidence rates, standardised to the WHO standard European population.

Supplementary Figure 3
Random-effects meta-analysis of population-screening incidence studies in the elderly. Note: the scale is different from Figure 2.

Supplementary Appendix 1: Search strategies

Period 1, up to March 2009

Medline search strategy

1 Exp parkinsonian disorders/
2 Parkinson$.tw.
3 1 or 2
4 incidence/ or incidence studies/
5 registries/
6 (incidence or incident or registr$ or register$).tw.
7 4 or 5 or 6
8 3 and 7
9 *parkinson disease/ep
10 exp *parkinson, secondary/ep
11 9 or 10
12 8 or 11

Embase search strategy

1 parkinson disease/
2 parkinson$.tw.
3 1 or 2
4 incidence/
5 epidemiological data/
6 population research/
7 geographic distribution/
8 register/
9 (incidence or incident or register$ or registr$ or new cases).mp*
10 4 or 5 or 6 or 7 or 8 or 9
11 3 and 10
12 *parkinson disease/ep
13 11 or 12

Period 2, 2009 to September 2017

Medline search strategy

1. Parkinson's disease/
2. Parkinsonian disorders/
3. Parkinson$.tw.
4. 1 or 2 or 3
5. Incidence/
6. Cohort studies/
7. Incidence.tw.
8. Epidemiology.tw.
9. Registries/
10. Register$.tw.
11. 8 or 9 or 10
12. 4 and 11
13. Parkinson disease/ep
14. 12 or 13
15. Animals not humans
16. 15 not 16

Embase search strategy

1. Parkinson disease/
2. Parkinsonism/
3. Parkinson$.tw.
4. 1 or 2 or 3
5. Incidence/
6. Incidence.tw.
7. Epidemiology/
8. Epidemiology.tw.
9. Registry/
10. Regist$.tw.
11. 5 or 6 or 7 or 8 or 9 or 10
12. 4 and 11
13. Parkinson disease/ep
14. 12 or 13
15. Animals not humans/
16. 14 not 15

Supplementary appendix 2: Quality criteria

Study	1. Whole population or random sample	2. Pop size <1 million with total person-years >1 million	3. Prospective?	4. Multiple sources to identify cases, including community	5. Review by study specialist to confirm diagnosis >70% of cases	6. Incidence defined by diagnosis (except for screening studies)	7. Appropriate diagnostic criteria	8. FU by study specialist to review diagnosis	9. Adequate reporting	10. Clear separation of incident and prevalent cases	Total number of criteria met
Morens 1996	0	0	1	1	1	1	1	0	1	1	**7**
Granieri 1991	1	1	0	1	1	0	1	0	1	1	**7**
Bower 1999	1	0	0	1	0	0	1	0	0	1	**4**
Wang 1991	1	0	1	1	1	1	1	0	0	0	**6**
Fall 1996	1	0	0	1	1	0	1	0	0	0	**4**
Sutcliffe 1995	1	1	0	1	1	0	1	0	0	0	**5**
Kuopio 1999	1	0	0	1	0	0	1	0	1	0	**4**
Mayeux 1995	1	0	1	1	1	0	1	0	1	1	**7**
Kusumi 1996	1	0	0	1	0	0	1	0	0	0	**3**
Taba 2003)	1	1	1	1	1	0	1	0	0	1	**7**
Cockerell 1996	1	0	1	0	0	0	0	0	0	1	**3**
Chen 2001	1	0	1	1	0	1	1	0	0	1	**6**
Van Den Eeden 2003	0	0	0	0	0	1	1	0	1	1	**4**
Vines 1999	1	1	0	1	0	1	1	0	1	0	**6**
MacDonald 2000	1	0	1	1	1	1	1	0	0	1	**7**
Foltynie 2004)	1	1	1	1	1	1	1	0	1	1	**9**
Alves 2009	1	0	1	1	1	1	1	0	1	1	**8**
Mehta 2007	1	0	0	0	0	1	0	0	1	1	**4**
Tan 2007	1	0	0	1	0	1	0	0	1	1	**5**
Wermuth 2008	1	0	0	1	0	1	1	0	0	0	**4**
Caslake 2013	1	1	1	1	1	1	1	1	1	1	**10**
Hristova 2009	1	1	1	1	1	1	1	0	1	1	**9**
Yamawaki 2009	1	0	0	0	0	0	1	0	0	0	**2**
Das 2010	1	0	1	1	1	0	1	1	1	1	**8**
Linder 2010	1	0	1	1	1	1	1	1	1	1	**9**
Winter 2010	1	0	1	1	1	0	1	1	1	1	**8**
Bauso 2012	1	0	0	0	0	1	1	0	1	1	**5**
Savica 2013	1	1	0	1	0	0	1	0	1	1	**6**
Duncan 2014	1	1	1	1	1	1	1	1	1	1	**10**
Gordon 2015	1	1	0	0	0	1	1	0	1	0	**5**
Evans 2016	1	1	1	1	1	1	1	1	0	1	**9**
De Lau 2004	1	0	1	1	1	1	1	1	1	1	**9**
Baldereschi 2000	1	0	1	1	0	1	1	0	1	1	**7**
Benito-Leon 2004	1	0	1	1	0	1	1	0	1	1	**7**
Perez 2010	1	0	1	1	0	1	1	0	0	1	**6**
Derweesh 2016	1	0	1	1	1	1	1	0	1	1	**8**

Quality criteria are based on the features of a good incidence study described by Twelves et al 2003 and the quality criteria for incidence or prevalence studies suggested by Loney et al 1998.

Descriptors of quality criteria:

1. Whole population studied or random sample drawn from whole population.
2. Study population size <1 million with total person-years >1 million.
3. Prospective study.
4. Multiple sources used to identify cases, with methods identifying cases in the community as well as in hospital.
5. Review by study specialist to confirm diagnosis in at least 70% of cases. Review by treating physicians was not sufficient to meet this criterion.
6. Incidence defined by diagnosis (except for screening studies in which definition by onset is more appropriate.
7. Appropriate diagnostic criteria
8. Follow-up by study specialist to review diagnosis.
9. Adequate reporting (population described, incident cases and denominator described by age stratum, confidence intervals reported for incidence rates).
10. Appropriate methods used to ensure prevalent cases not included in incidence rate.

Journal	Year	Month	First author	Mean age at onset or diagnosis (NS= not stated
Movement Disorders	2016	December	Willis	77.5
Movement Disorders	2016	December	Lord	68.5
Movement Disorders	2016	December	Delval	58.3
Movement Disorders	2016	December	Wessel	NS
Movement Disorders	2016	December	Polli	56.1
Movement Disorders	2016	December	Goetz	NS
Movement Disorders	2016	December	Hughes	NS
Movement Disorders	2016	December	Tan	60.0
Movement Disorders	2016	December	Svensson	73.0
Movement Disorders	2016	December	Pyle	NS
Movement Disorders	2016	December	Foo	63.7
Movement Disorders	2016	December	Mangesius	58.6
Movement Disorders	2016	November	Berman	56.0
Movement Disorders	2016	November	Varanda	59.0
Movement Disorders	2016	November	Neumann	49.0
Movement Disorders	2016	October	Macleod	72.5
Movement Disorders	2016	October	Rascol	61.5
Movement Disorders	2016	October	Tessitore	60.5
Movement Disorders	2016	October	Huppertz	56.9
Movement Disorders	2016	October	Malek	66.2
Movement Disorders	2016	October	Mirelman	59.0
Movement Disorders	2016	October	Majbour	59.4
Movement Disorders	2016	October	Fraser	57.0
Movement Disorders	2016	October	Hirschmann	58.7
Movement Disorders	2016	October	Antunes	60.9
Movement Disorders	2016	October	Mestre	48.0
Movement Disorders	2016	October	Kim	NS
Movement Disorders	2016	October	van Uem	52
Movement Disorders	2016	September	LeWitt	52.9
Movement Disorders	2016	September	Hauser	NS
Movement Disorders	2016	September	Tison	52.3
Movement Disorders	2016	September	Fleury	50.0
Movement Disorders	2016	September	Malkneccht	53.0
Movement Disorders	2016	September	Rossi	64.1
Movement Disorders	2016	September	Nakamura	61.5
Movement Disorders	2016	September	Svenningsson	NS
Movement Disorders	2016	September	Sankar	NS
Movement Disorders	2016	August	Zhang	56.7
Movement Disorders	2016	August	McIntosh	NS
Movement Disorders	2016	August	Dams	NS
Movement Disorders	2016	August	Marras	58.7
Movement Disorders	2016	August	Nackaerts	55.6
Movement Disorders	2016	August	Steigerwald	NS
Movement Disorders	2016	August	Marras	NS
Movement Disorders	2016	July	Shrestha	69.0
Movement Disorders	2016	July	Flores-Cuadrado	56.3
Movement Disorders	2016	July	Williams-Gray	65.8

Movement Disorders	2016	July	Caviness	NS	
Movement Disorders	2016	July	Loane	NS	
Movement Disorders	2016	July	Kluger	NS	
Movement Disorders	2016	July	Trenkwalder	NS	
Movement Disorders	2016	July	Trenkwalder	NS	
Movement Disorders	2016	July	Breen		63.4
Parkinsonism & Related Disorders	2016	December	Fisher		59.1
Parkinsonism & Related Disorders	2016	December	Zhu		50.5
Parkinsonism & Related Disorders	2016	December	Lucas-Jimenez		61.0
Parkinsonism & Related Disorders	2016	December	Merola		58.6
Parkinsonism & Related Disorders	2016	December	Rolston	NS	
Parkinsonism & Related Disorders	2016	December	Vanbellingen		61.4
Parkinsonism & Related Disorders	2016	December	Bernhardt	NS	
Parkinsonism & Related Disorders	2016	December	Boel		48.5
Parkinsonism & Related Disorders	2016	December	Lawton		66.1
Parkinsonism & Related Disorders	2016	December	Mills		62.2
Parkinsonism & Related Disorders	2016	December	Mills		59.3
Parkinsonism & Related Disorders	2016	December	Tatura	NS	
Parkinsonism & Related Disorders	2016	December	Dan		57.3
Parkinsonism & Related Disorders	2016	December	Wills	NS	
Parkinsonism & Related Disorders	2016	November	Biernacka	NS	
Parkinsonism & Related Disorders	2016	November	Fielding		71.9
Parkinsonism & Related Disorders	2016	November	Ricciardi		60.6
Parkinsonism & Related Disorders	2016	November	Unger		60.9
Parkinsonism & Related Disorders	2016	November	Hattori		60.2
Parkinsonism & Related Disorders	2016	November	Martino	NS	
Parkinsonism & Related Disorders	2016	November	lee		61.3
Parkinsonism & Related Disorders	2016	November	Moccia		62.8
Parkinsonism & Related Disorders	2016	November	Hand		69.4
Parkinsonism & Related Disorders	2016	November	Kotagal		58.6
Parkinsonism & Related Disorders	2016	October	Tacik		67.0
Parkinsonism & Related Disorders	2016	October	Foo		60.7
Parkinsonism & Related Disorders	2016	October	Lee		67.1
Parkinsonism & Related Disorders	2016	October	Ucak	NS	
Parkinsonism & Related Disorders	2016	October	Goldstein		58.2
Parkinsonism & Related Disorders	2016	October	Rajput		70.8
Parkinsonism & Related Disorders	2016	October	Siepmann	NS	
Parkinsonism & Related Disorders	2016	September	Krishnamoorthy		49.1
Parkinsonism & Related Disorders	2016	September	Schiehser		59.1
Parkinsonism & Related Disorders	2016	September	Premi		66.1
Parkinsonism & Related Disorders	2016	September	Narayanaswami	NS	
Parkinsonism & Related Disorders	2016	August	Palhagen		51.8
Parkinsonism & Related Disorders	2016	August	Goh		67.3
Parkinsonism & Related Disorders	2016	August	Yang		57.7
Parkinsonism & Related Disorders	2016	August	Arnaldi		70.4
Parkinsonism & Related Disorders	2016	August	Sleeman		71.8
Parkinsonism & Related Disorders	2016	August	Wang		59.4
Parkinsonism & Related Disorders	2016	August	Pereira	NS	
Parkinsonism & Related Disorders	2016	August	Rektorova		58.2
Parkinsonism & Related Disorders	2016	August	Cilia		52.0

Parkinsonism & Related Disorders	2016	August	Merola		49.8
Parkinsonism & Related Disorders	2016	August	Rengmark		57.8
Parkinsonism & Related Disorders	2016	August	Mengel		60.0
Parkinsonism & Related Disorders	2016	July	Svensson	NS	
Parkinsonism & Related Disorders	2016	July	Zhang		58.4
Parkinsonism & Related Disorders	2016	July	Simuni		60.6
Parkinsonism & Related Disorders	2016	July	Peretz		71.3
Parkinsonism & Related Disorders	2016	July	Vervoort		53.8
Parkinsonism & Related Disorders	2016	July	Maskova		34.5
Parkinsonism & Related Disorders	2016	July	Podgorny		62.0
Parkinsonism & Related Disorders	2016	July	Warnecke		58.0
Parkinsonism & Related Disorders	2016	July	Ruzicka		55.0
Parkinsonism & Related Disorders	2016	July	Shih		66.6
Parkinsonism & Related Disorders	2016	July	Macleod		72.5
Parkinsonism & Related Disorders	2016	July	van Balkom		58.0
Parkinsonism & Related Disorders	2016	July	Erro		63.2
Parkinsonism & Related Disorders	2016	July	Kaipa	NS	
Parkinsonism & Related Disorders	2016	July	Choubtum	NS	
Brain	2016	October	Kinan		61.4
Brain	2016	September	Accolla		47.3
Brain	2016	September	Maillet		57.1
Brain	2016	August	Rae		59.6
Brain	2016	August	Kondylis	NS	
Brain	2016	August	Rolinski		65.2
Brain	2016	August	Rae		59.6
Brain	2016	July	Hansen		62.6
Brain	2016	July	Masellis		57.7
Neurology	2016	December	Pyatigorskaya		53.5
Neurology	2016	December	Pagano		56.8
Neurology	2016	November	Mattis	NS	
Neurology	2016	November	Brys		54.5
Neurology	2016	October	Bjornestad		67.5
Neurology	2016	October	Morgante		
Neurology	2016	September	Barichella		60.9
Neurology	2016	August	Burciu		60.9
Neurology	2016	August	Gibbons		56.81785714
Neurology	2016	July	Mollenhauer		61.59166667
JNNP	2016	December	Little		47
JNNP	2016	November	Swallow		66.2
JNNP	2016	October	Kraemmer		64.51416667
JNNP	2016	October	McMillen		61
JNNP	2016	September	Moisan		76
JNNP	2016	September	Evans		68.6
JNNP	2016	August	Smith		61.7
JNNP	2016	July	Yamada		53.5
JNNP	2016	July	Little		41.8

Excluded?	Reason for exclusion, if applicable
Excluded	Only 60+
Excluded	DBS patients
Excluded	DBS patients
Excluded	DBS patients
Excluded	Patietns treated with DBS
Excluded	Patients with dyskinesias (more common in young-onset PD)
Excluded	Patietns treated with DBS
Excluded	Patients treated with DBS
Excluded	Advanced therapies paper
Excluded	Patients treated with DBS
Excluded	Some age restriction

Excluded	Patietns treated with DBS
Excluded	Patietns treated with DBS
Excluded	Data not available for PD separately from other causes of parkinsonism
Excluded	Cases of conjugal PD
Excluded	Patients with LCIG
Excluded	Restricted to 45-75 yrs at inclusion

Excluded	Advanced therapies paper
Excluded	Early-onset PD
Excluded	Patietns treated with DBS
Excluded	Patients age-matched to idiopathic RBD patients
Excluded	Parkin-associated
Excluded	Patietns treated with DBS
Excluded	Patietns treated with DBS

Study Geographical area (Populaton size)	Incidence period	Sources to identify possible cases	Methods of case identification (% possible cases examined by study specialist)	Definition of incident cases	Diagnostic criteria	Prospective?	Quality assessment score	Number of cases	Crude incidence rate per 100,000 person years (95% CI)	Mean age at inception (95% CI)
Morens 1996[1] Hawaii (Cohort of 8,006 men aged 45-95)	1965-1994	Medical records (hospital, neurology), death certificates, re-screening of cohort with questionnaire, examination	Case notes review Examination by neurologist (NS)	Diagnosis	≥2 cardinal signs, improvement after levodopa, relevant exclusions	Partial	7	92	11.1	NS
Granieri 1991[2] Ferrara, Italy (187,381)	1967-1987	Medical records (hospital, rehabilitation centres, neurology); health insurance records; nursing homes; drug prescriptions; GP telephone survey	Case notes review Examination by neurologist (32)	Onset	≥2 of 4 cardinal signs, progressive deterioration, relevant exclusions	No	7	394	10.0 (9.1-11.1)	62.6 (61.7–63.5) at onset
Bower 1999[3] Olmsted County, USA (NS)	1976-1990	Medical records (Mayo clinic record linkage)	Case notes review (0)	Onset	≥2 of 4 cardinal signs, all of: (i) response to levodopa, (ii) no prominent/early signs of atypical syndrome, (iii) no secondary cause	No	4	154	10.8	NS
Wang 1991[4] China (3,869,162)	1986	Door-to-door questionnaire distributed by medical workers	Examination by neurologist (100)	Diagnosis	Insidiously progressive rest tremor, rigidity, hypokinesia, cases without definite cause, onset after middle age. Relevant exclusions	Yes	6	58	1.5	NS
Fall 1996[5] Southeast Sweden (147,777)	1986-1988	Medical records (neurology); inquiries to all neurologists, geriatricians, GPs; drug prescriptions; nursing homes	Case notes review Examination by neurologist if not previously seen by expert (NS)	Onset	All of: (i) At least 1 of: tremor, rigidity, hypokinesia, (ii) progression, (iii) no neuroleptics (iv) response to levodopa	No	4	49	11	65.6 (63.7–67.5) at onset
Sutcliffe 1995[6] Northampton, UK (298,985)	1986-1990	Medical records (hospital), enquiries to GPs, consultants	Examination by neurologist of all patients consented, Case notes review of those refusing (89)	Onset	UKPDBB criteria	No	5	175	12	NS
Kuopio 1999[7] Turku, Finland (196,864)	1987-1991	Medical records (neurology, hspital), Finnish PD association, residential homes Inquiries to health centres, social insurance records	Case notes review and examination by neurologist of doubtful cases (39)	NS	UKPDBB criteria	No	4	NS	17.2	NS
Mayeux 1995[8]	1989-1991	Medical records (HMO,	Examination by	Onset	UKPDBB criteria	Yes	7	83	13 (10.2-	76.3 (74.3-

Study Geographical area (Populaton size)	Incidence period	Sources to identify possible cases	Methods of case identification (% possible cases examined by study specialist)	Definition of incident cases	Diagnostic criteria	Prospective?	Quality assessment score	Number of cases	Crude incidence rate per 100,000 person years (95% CI)	Mean age at inception (95% CI)
Manhattan,USA (NS)		hospital, private GP, neurology); social services; disability / pension records; nursing homes; health Insurance records	neurologist to confirm diagnosis (100)						15.8)	78.3) at diagnosis 75.2 (73.2-77.2) at onset
Kusumi 1996[9] Yonago City, Japan (132,315)	1989-1992	Medical records (hospital); questionnaire (other hospitals, medical practitioners), disability records, death certificates	Not specified (0)	Onset	≥ 2 of 4 cardinal signs, Improvement after levodopa, and relevant exclusions	No	3	79	5	70.4 (68.5-72.3) at onset
Taba 2003[10] Tartu, Estonia (156,417)	1990-1998	Neurology and neurosurgery records reviewed yearly, GPs asked to notify, nursing homes and regional hospitals visited, PD Society contacted, prescription data	Examination by neurologist (100)	Onset	UKPDBB criteria	Yes	7	264	18.8	68.8 (67.7-69.9) at onset
Cockerell 1996[11] London, UK (26,636)	1993	Recording of GPs consultations for neurological problems, GP notes screening in a proportion	Review of information sent by GP, Neurology referral encouraged (NS)	NS	NS	Yes	3	7	PD 26	NS
Chen 2001[12] Ilan County, Taiwan (75,579)	1993-1997	Door-to-door questionnaire +/- examination to identify people without Parkinsonism at baseline. New cases then identified from Bureau of National Health Insurance records	Case notes review (0)	Diagnosis	≥ 2 of 4 cardinal signs plus exclusions	Yes	6	15	10.4	NS
Van Den Eeden 2003[13] Northern California, USA (4,776,038 person-years)	1994-1995	Regular surveillance of computer databases (outpatient/inpatient utilization/billing, pharmacy); notification of all neurologists asking for referrals	Case notes review by movement disorders specialist (0)	Diagnosis	Modified CAPIT/Hughes diagnostic criteria	No	4	588	12.3	70.5 (70.2–73.8) at diagnosis
Viñes 1999[14] Navarra, Spain (523,563)	1994-1995	Medical records (neurologists, GPs); questionnaire to neurologists; telephone inquiries to residential care doctors	Case notes review (NS)	Diagnosis	UKPDBB criteria	Unclear	6	86	8.21	PD 69.5 (67.9-71.3) at onset
MacDonald 2000[15] London, UK	1995-1996	Medical records (all GP notes screened, hospital); drug	GP case notes review, examination by	Diagnosis	≥ 2 of 4 cardinal signs with relevant exclusions	Yes	7	NS	19	NS

Study Geographical area (Populaton size)	Incidence period	Sources to identify possible cases	Methods of case identification (% possible cases examined by study specialist)	Definition of incident cases	Diagnostic criteria	Prospective?	Quality assessment score	Number of cases	Crude incidence rate per 100,000 person years (95% CI)	Mean age at inception (95% CI)
(100,230)		prescriptions; GP referrals (any neurological cases) to linkage clinic; enquiries to GPs; GP databases	neurologist (100)							
Foltynie 2004[16] Cambridgeshire, UK (700,000)	2000-2002	Regular requests to, GPs, neurologists, geriatricians, PD nurses; hospital discharge coding; advertising through PD Society	Examination by neurologist (77)	Diagnosis	UKPDBB criteria	Yes	9	201	13.6 (11.8-15.6)	72.0 (70.2-73.8) at diagnosis
Alves 2009[17] Western Norway (1,052,075)	2004-2006	Direct referral with email reminders (GP, hospital doctors); nursing homes; medical records (hospital, GP); hand search of referrals	Examination by study neurologist (99.8)	Diagnosis	≥2 of 4 cardinal signs with relevant exclusions	Yes	8	265	13.7 (12.2-15.5)	69.4 (68.4-70.4) at diagnosis
Wermuth 2008[18] Faroe Islands (45,878)	1995-2005	Direct referral with reminders (GP, Neurologists), drug register, self-referral, press release	Examination by study neurologist (66.7)	Diagnosis	≥2 of 3 cardinal signs without secondary cause	No	4	97	21.1 (17.3-25.8)	66.0 at onset
Caslake 2013[19] Aberdeen, UK (317,357 [Pilot phase 148,600])	2002-2004; 2006-2009	Direct referral with email reminders to GPs, hospital doctors; medical records (hospital, GP); hand search of referrals	Examination by study neurologist (97.7)	Diagnosis	≥2 of 4 cardinal signs, clinical diagnosis of PD, not drug-induced	Yes	10	201	17.5 (15.1-19.9)	72.3 (70.9-73.7) at diagnosis
Hristova 2010[20] Southern Bulgaria (713,090)	2002-2004	Repeated survey with a validated questionnaire; nursing home surveys; medical records from regional hospitals.	Examination by a specialist plus ancillary tests (100)	Diagnosis	UKPDBB criteria plus levodopa challenge	Yes	9	244	11.4 (10.1-13.0)	68 (66-70) at onset
Yamawaki 2009[21] Western Japan (113,191)	2000-2004	Medical records (hospital); questionnaire to other hospitals and medical practitioners, disability records, death certificates	Not specified (0)	Onset	UKPDBB criteria	No	2	254	18.7 (11.3–25.5)	68.7 (67.4-70.0) at onset
Das 2010[22] Kolkata, India (100,802)	2003-2007	Repeated survey of the study population selected through stratified random and alternate sampling, validated questionnaire.	Examination by a specialist (100)	Onset	UKPDBB criteria	Yes	8	23	4.56 (2.87-7.51)	NS
Linder 2010[23] Umea, Sweden	2004-2007	Direct referral with email reminders to GPs, hospital	Examination by a specialist,	Diagnosis	UKPDBB criteria	Yes	9	112	19.7 (16.1–23.3)	70.8 (68.9-72.7) at

Study Geographical area (Populaton size)	Incidence period	Sources to identify possible cases	Methods of case identification (% possible cases examined by study specialist)	Definition of incident cases	Diagnostic criteria	Prospective?	Quality assessment score	Number of cases	Crude incidence rate per 100,000 person years (95% CI)	Mean age at inception (95% CI)
(141,950)		doctors, nursing homes; hand searching of GP outpatient referrals; survey of nursing homes; medical records	neuroimaging, second specialist opinion where necessary. (100)							diagnosis
Winter 2010[24] Moscow (1,237,900)	2006-2008	Medical Record Direct referral with email reminders GP, Hospital doctors, Nursing homes.	Examination by specialist performed, neuroimaging (100)	Onset	UKPDBB criteria	Yes	8	308	9.95 (8.87 – 11.13)	64.6 (63.5-65.7) at onset
Bauso 2012[25] Buenos Aires, Argentina (140,000)	2003-2008	Medical Record Drug register Database searches.	Case note review and further information from treating doctors (0)	Diagnosis	UKPDBB criteria	No	5	239	31.2 (27.4-35.4)	71.5 (70.1-72.9) at diagnosis
Savica 2013[26] Olmsted County, USA (NS)	1991-2005	Medical records linkage system, Rochester Epidemiology Project	Review of medical records (0)	Onset	≥2 cardinal signs with relevant exclusions	No	6	264	14.2 (12.6-16.0)	71 (69-73) at diagnosis
Duncan 2014[27] Newcastle, UK (488,576)	2009-2011	GP, neurologist, geriatrician and PD nurse specialist referrals, regular reminders; screening of GP lists	Examination by specialist + FP-CIT SPECT if unclear (NS)	Diagnosis	UKPDBB criteria	Yes	10	155	15.9 (13.4-18.4)	72.4 (70.8-74.0) at diagnosis
Gordon 2015[28] Navajo Nation, USA (200,000)	2002-2011	Database searches. Drug register	Case note review and contact with managing physician (0)	Diagnosis	UKPDBB criteria	No	5	524	22.5 (20.7-24.5)	74 (IQR 66-80) at diagnosis
Evans 2016[29] Cambridgeshire, UK (approx. 620,000)	2008-2010	Screen of NHS referrals, contacting GPs and hospital specialists,	Examination by neurologist	Diagnosis	UKPDBB criteria	Yes	9	173	15.9 (13.8-18.2)	68.6 at diagnosis (67.6 at onset)
Screening studies in older age groups										
De Lau 2004[30] Rotterdam, The Netherlands (6,839 aged 55 years or over)	1990-1999	In person screening of whole cohort (78% completed screening) at baseline and follow-up (mean follow-up 5.8 years). Also computer linkage to GP and pharmacy records.	Examination by neurologist (87)	Midpoint between examination at which parkinsonian, and prev examination	≥2 of 4 cardinal signs with relevant exclusions	Yes	8	67	174 (140-220)	
Baldereschi 2000[31] Italy (4,341 aged 65-84 years)	1992-1996	In person screening of random sample of population at baseline (82% completed screening) and follow-up	Examination by neurologist (NS)	Onset	≥2 of 4 cardinal signs with relevant exclusions	Yes	7	42	346 (241-450)	

Study Geographical area (Populaton size)	Incidence period	Sources to identify possible cases	Methods of case identification (% possible cases examined by study specialist)	Definition of incident cases	Diagnostic criteria	Prospective?	Quality assessment score	Number of cases	Crude incidence rate per 100,000 person years (95% CI)	Mean age at inception (95% CI)
		(mean follow-up 3.9 years). Also data from records, relatives and GPs								
Benito-Leon 2004[32] Central Spain (5,160 aged 65 years or over)	1994-1998	Screening of whole cohort using questionnaire at baseline (71% completed screening)and follow-up (mean follow-up 3 years). Also computer linkage to GP and pharmacy records.	Structured clinical work-up by neurologists, then discussion by panel of 3 senior neurologists (27)	Onset	UKPDBB criteria	Yes	7	17	133 (83-215)	
Mehta 2007[33] Blue Mountains, Australia (2,545)	1992-2002	Repeated cross- sectional survey in residents aged 49 years and older.	Case notes review (0)	Diagnosis	Clinical features consistent with PD	No	4	19	81 (44-117)	
Perez 2010[34] Gironde and Dordogne, France (3777 aged 65 and over)	15 years from c. 1988	Repeated in-person screening of random sample of cohort at baseline (68% completed screening) and repeated follow-up up to 15 years.	GP and specialist records reviewed if screen positive. Some reviewed by study neurologist (~60)	Onset	UKPDBB criteria	Yes	6	68	263 (207-334)	
Darweesh 2016[35] Rotterdam, Netherlands (4472 aged 55 or over)	2000-2011	In person screening of whole cohort (78% completed screening) at baseline and follow-up). Also computer linkage to GP and pharmacy records.	UPDRS examination and review by neurologist	Onset	Good treatment response or positive DaTSCAN or diagnosis confirmed by a neurologist with exclusions for secondary parkinsonism	Yes	8	10	45 (22-83)	

CI = confidence interval; NS = not stated; UKPDBB = United Kingdom Parkinson's Disease Brain Bank; UPDRS = Unified Parkinson's disease rating scale.

Reference to included studies

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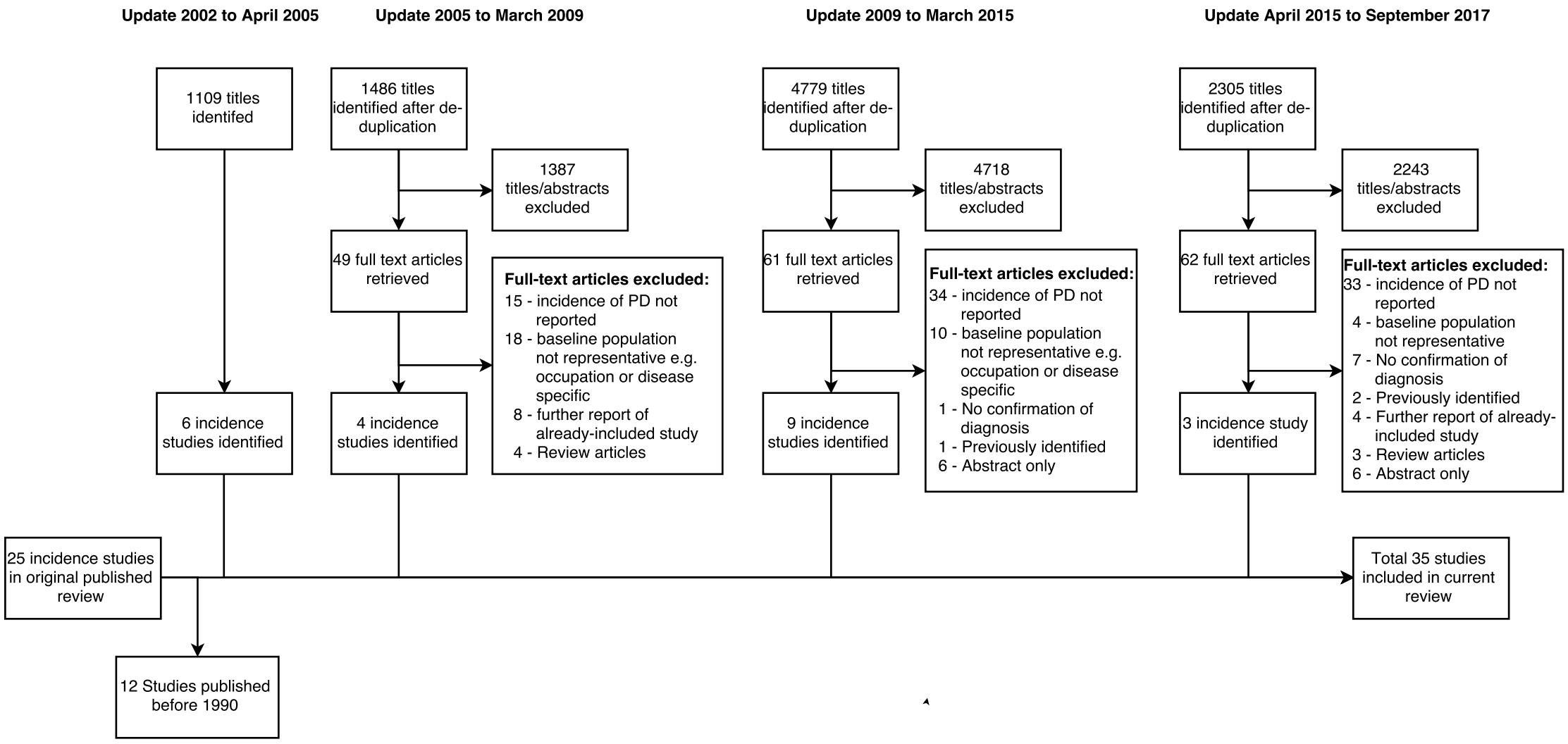
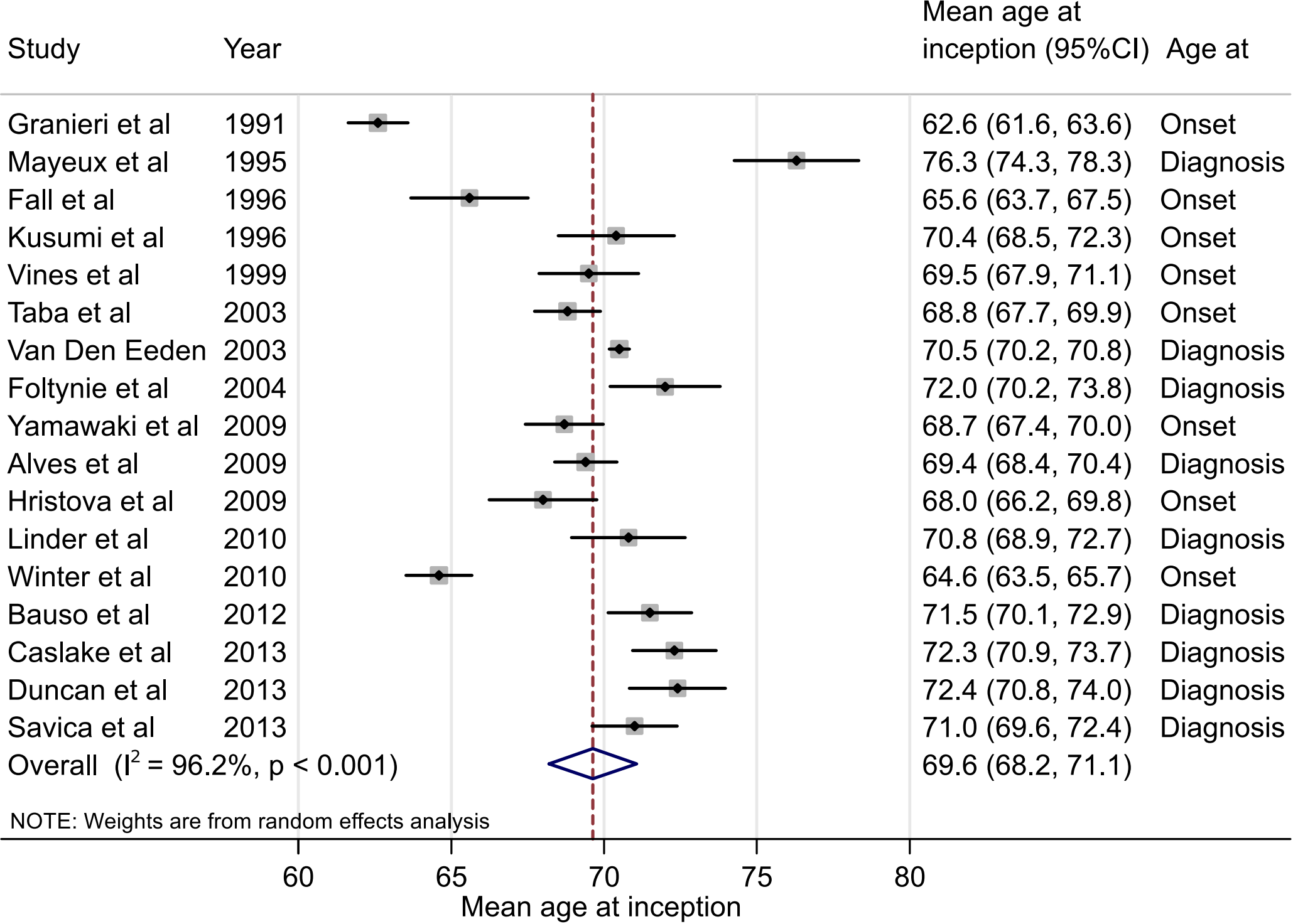
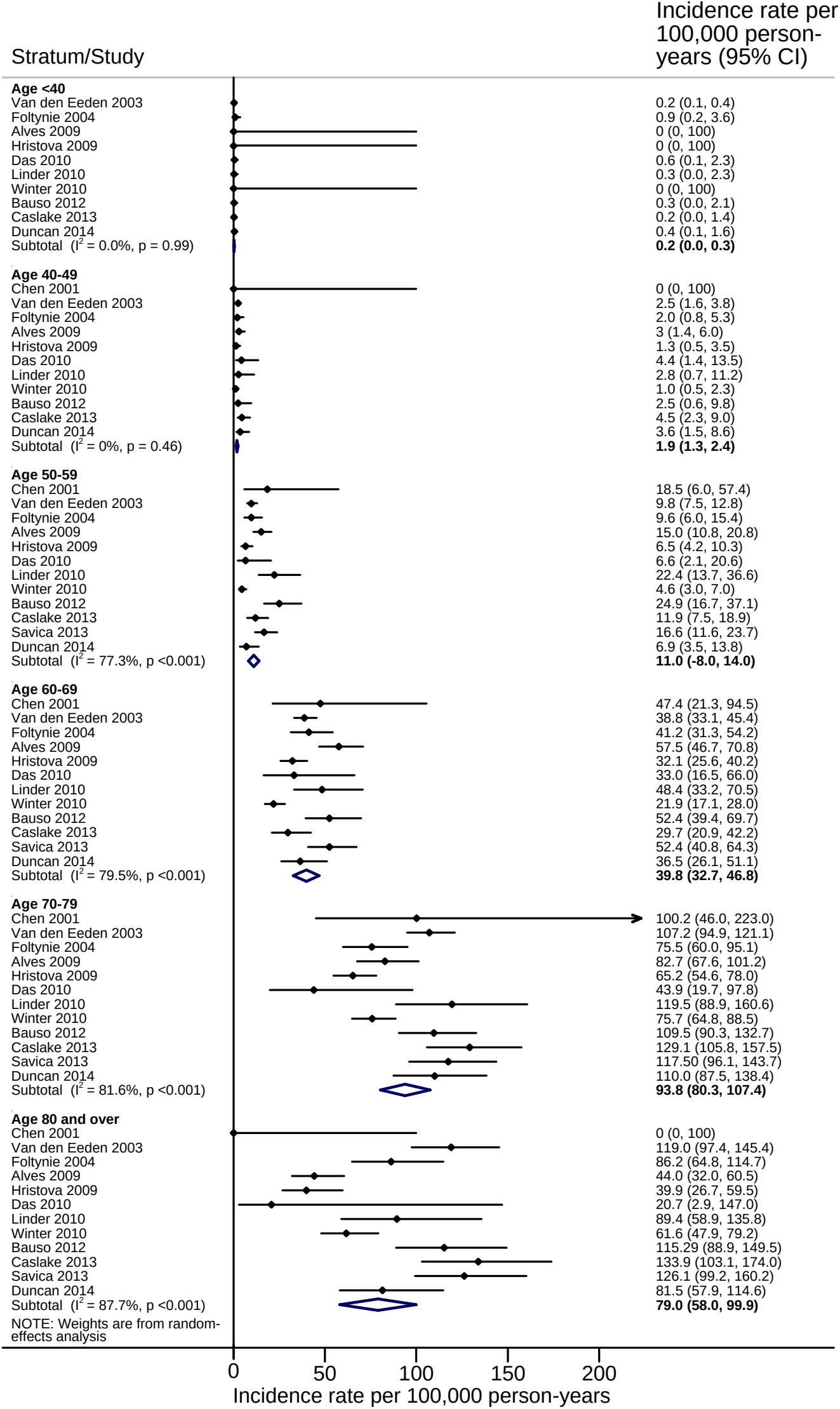
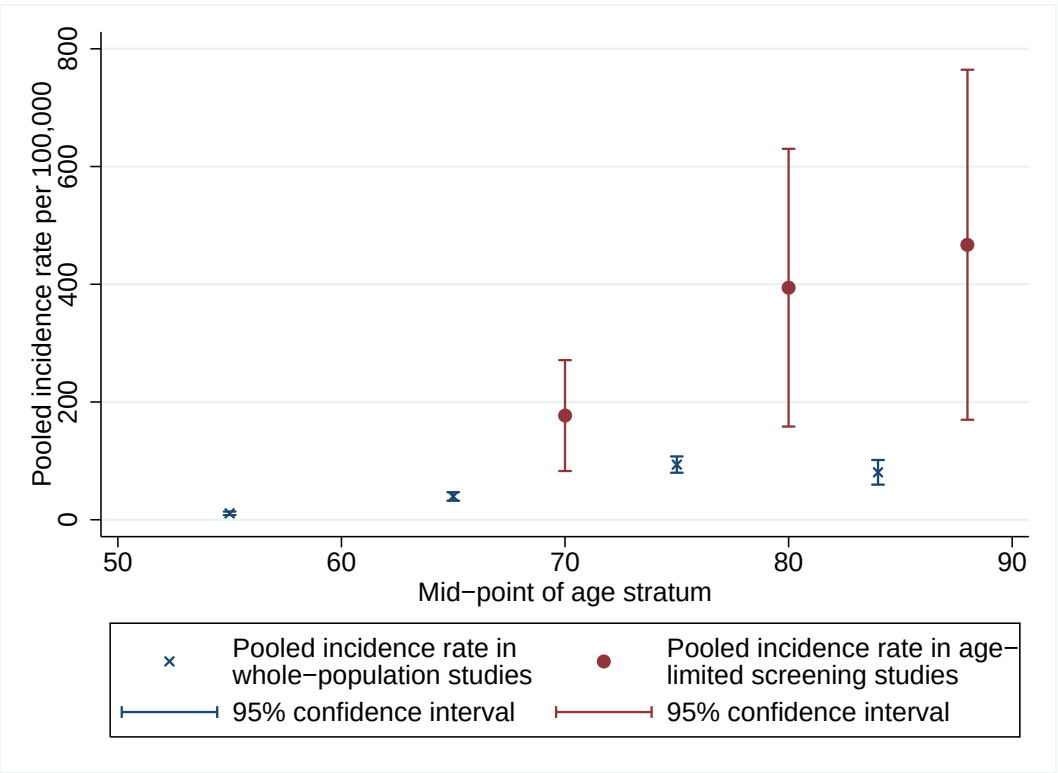

Update 2002 to April 2005
Update 2005 to March 2009
Update 2009 to March 2015
Update April 2015 to September 2017
1109 titles identifed
1486 titles identified after de-duplication
1387 titles/abstracts excluded
49 full text articles retrieved
Full-text articles excluded:
15 - incidence of PD not reported
18 - baseline population not representative e.g. occupation or disease specific
8 - further report of already-included study
4 - Review articles
6 incidence studies identified
4 incidence studies identified
4779 titles identified after de-duplication
4718 titles/abstracts excluded
61 full text articles retrieved
Full-text articles excluded:
34 - incidence of PD not reported
10 - baseline population not representative e.g. occupation or disease specific
1 - No confirmation of diagnosis
1 - Previously identified
6 - Abstract only
9 incidence studies identified
2305 titles identified after de-duplication
2243 titles/abstracts excluded
62 full text articles retrieved
Full-text articles excluded:
33 - incidence of PD not reported
4 - baseline population not representative
7 - No confirmation of diagnosis
2 - Previously identified
4 - Further report of already-included study
3 - Review articles
6 - Abstract only
3 incidence study identified
25 incidence studies in original published review
Total 35 studies included in current review
12 Studies published before 1990


Study
Year
Mean age at inception (95%CI)
Age at
Granieri et al 1991 62.6 (61.6, 63.6) Onset
Mayeux et al 1995 76.3 (74.3, 78.3) Diagnosis
Fall et al 1996 65.6 (63.7, 67.5) Onset
Kusumi et al 1996 70.4 (68.5, 72.3) Onset
Vines et al 1999 69.5 (67.9, 71.1) Onset
Taba et al 2003 68.8 (67.7, 69.9) Onset
Van Den Eeden 2003 70.5 (70.2, 70.8) Diagnosis
Foltynie et al 2004 72.0 (70.2, 73.8) Diagnosis
Yamawaki et al 2009 68.7 (67.4, 70.0) Onset
Alves et al 2009 69.4 (68.4, 70.4) Diagnosis
Hristova et al 2009 68.0 (66.2, 69.8) Onset
Linder et al 2010 70.8 (68.9, 72.7) Diagnosis
Winter et al 2010 64.6 (63.5, 65.7) Onset
Bauso et al 2012 71.5 (70.1, 72.9) Diagnosis
Caslake et al 2013 72.3 (70.9, 73.7) Diagnosis
Duncan et al 2013 72.4 (70.8, 74.0) Diagnosis
Savica et al 2013 71.0 (69.6, 72.4) Diagnosis
Overall (I^2 = 96.2%, p < 0.001) 69.6 (68.2, 71.1)
NOTE: Weights are from random effects analysis
60
65
70
75
80
Mean age at inception


Stratum/Study
Incidence rate per 100,000 person-years (95% CI)
Age <40
Van den Eeden 2003
Foltynie 2004
Alves 2009
Hristova 2009
Das 2010
Linder 2010
Winter 2010
Bauso 2012
Caslake 2013
Duncan 2014
Subtotal (I² = 0.0%, p = 0.99)
0.2 (0.1, 0.4)
0.9 (0.2, 3.6)
0 (0, 100)
0 (0, 100)
0.6 (0.1, 2.3)
0.3 (0.0, 2.3)
0 (0, 100)
0.3 (0.0, 2.1)
0.2 (0.0, 1.4)
0.4 (0.1, 1.6)
0.2 (0.0, 0.3)
Age 40-49
Chen 2001
Van den Eeden 2003
Foltynie 2004
Alves 2009
Hristova 2009
Das 2010
Linder 2010
Winter 2010
Bauso 2012
Caslake 2013
Duncan 2014
Subtotal (I² = 0%, p = 0.46)
0 (0, 100)
2.5 (1.6, 3.8)
2.0 (0.8, 5.3)
3 (1.4, 6.0)
1.3 (0.5, 3.5)
4.4 (1.4, 13.5)
2.8 (0.7, 11.2)
1.0 (0.5, 2.3)
2.5 (0.6, 9.8)
4.5 (2.3, 9.0)
3.6 (1.5, 8.6)
1.9 (1.3, 2.4)
Age 50-59
Chen 2001
Van den Eeden 2003
Foltynie 2004
Alves 2009
Hristova 2009
Das 2010
Linder 2010
Winter 2010
Bauso 2012
Caslake 2013
Savica 2013
Duncan 2014
Subtotal (I² = 77.3%, p <0.001)
18.5 (6.0, 57.4)
9.8 (7.5, 12.8)
9.6 (6.0, 15.4)
15.0 (10.8, 20.8)
6.5 (4.2, 10.3)
6.6 (2.1, 20.6)
22.4 (13.7, 36.6)
4.6 (3.0, 7.0)
24.9 (16.7, 37.1)
11.9 (7.5, 18.9)
16.6 (11.6, 23.7)
6.9 (3.5, 13.8)
11.0 (-8.0, 14.0)
Age 60-69
Chen 2001
Van den Eeden 2003
Foltynie 2004
Alves 2009
Hristova 2009
Das 2010
Linder 2010
Winter 2010
Bauso 2012
Caslake 2013
Savica 2013
Duncan 2014
Subtotal (I² = 79.5%, p <0.001)
47.4 (21.3, 94.5)
38.8 (33.1, 45.4)
41.2 (31.3, 54.2)
57.5 (46.7, 70.8)
32.1 (25.6, 40.2)
33.0 (16.5, 66.0)
48.4 (33.2, 70.5)
21.9 (17.1, 28.0)
52.4 (39.4, 69.7)
29.7 (20.9, 42.2)
52.4 (40.8, 64.3)
36.5 (26.1, 51.1)
39.8 (32.7, 46.8)
Age 70-79
Chen 2001
Van den Eeden 2003
Foltynie 2004
Alves 2009
Hristova 2009
Das 2010
Linder 2010
Winter 2010
Bauso 2012
Caslake 2013
Savica 2013
Duncan 2014
Subtotal (I² = 81.6%, p <0.001)
100.2 (46.0, 223.0)
107.2 (94.9, 121.1)
75.5 (60.0, 95.1)
82.7 (67.6, 101.2)
65.2 (54.6, 78.0)
43.9 (19.7, 97.8)
119.5 (88.9, 160.6)
75.7 (64.8, 88.5)
109.5 (90.3, 132.7)
129.1 (105.8, 157.5)
117.50 (96.1, 143.7)
110.0 (87.5, 138.4)
93.8 (80.3, 107.4)
Age 80 and over
Chen 2001
Van den Eeden 2003
Foltynie 2004
Alves 2009
Hristova 2009
Das 2010
Linder 2010
Winter 2010
Bauso 2012
Caslake 2013
Savica 2013
Duncan 2014
Subtotal (I² = 87.7%, p <0.001)
0 (0, 100)
119.0 (97.4, 145.4)
86.2 (64.8, 114.7)
44.0 (32.0, 60.5)
39.9 (26.7, 59.5)
20.7 (2.9, 147.0)
89.4 (58.9, 135.8)
61.6 (47.9, 79.2)
115.29 (88.9, 149.5)
133.9 (103.1, 174.0)
126.1 (99.2, 160.2)
81.5 (57.9, 114.6)
79.0 (58.0, 99.9)
NOTE: Weights are from random-effects analysis
0
50
100
150
200
Incidence rate per 100,000 person-years


Pooled incidence rate per 100,000
0
200
400
600
800
50
60
70
80
90
Mid−point of age stratum
Pooled incidence rate in whole−population studies
95% confidence interval
Pooled incidence rate in age−limited screening studies
95% confidence interval

Journal	Number of articles with a general sample of Parkinson's disease	Number of these articles reporting age at onset or age at diagnosis	Median of reported mean ages at inception[a] (IQR)	Mean of reported mean ages at inception[a] (SD)	Range of mean age at inception[a]
Parkinsonism & Related Disorders	55	43	60.6 (58.2–66.1)	61.5 (5.7)	49.1–72.5
Movement Disorders	42	29	59.0 (56.7–63.4)	60.2 (5.3)	52.0–73.0
Neurology	9	8	58.9 (55.7–61.2)	59.1 (4.6)	53.5–67.5
Journal of Neurology, Neurosurgery & Psychiatry	7	7	64.5 (56.7–63.4)	64.5 (5.3)	53.5–76.0
Brain	7	7	59.6 (57.1–61.4)	57.9 (5.1)	47.3–62.6
All five journals combined	120	94	60.4 (57.5–63.7)	60.8 (5.6)	47.3-76.0

[a]Either age at diagnosis or age at disease onset.