Published in final edited form as:

Neurobiol Aging. 2008 December ; 29(12): 1765–1773. doi:10.1016/j.neurobiolaging.2007.04.009.

Complete ascertainment of Parkinson disease in the Swedish Twin Registry

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Abstract

This report describes the ascertainment of Parkinson disease (PD) in all individuals aged 50 years or older (49,814 individuals) from the Swedish Twin Registry. In phase one of the study, all twins were screened for PD using telephone interviews, with a response rate of 72.7%. In phase two, twins with suspected PD were re-contacted to exclude anyone from follow-up who reported parkinsonian symptoms due to diseases other than PD. In the third phase, in-person clinical evaluations were completed for twins who were still considered PD suspects after phase two and for a sample of co-twins. During the clinical evaluations, we also collected blood samples and information about a variety of environmental exposures. Overall prevalence rate for PD was 496 per 100,000 individuals. Among the 132 PD cases identified, there were only three concordant twin pairs. In total 7.2% of PD cases reported a first degree relative with PD.

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Disclosure Statement

None of the authors has a conflict of interest. All procedures were performed according to the Declaration of Helsinki and the project was approved by the Regional Ethical Review Board in Stockholm and the University of Southern California IRB.

Keywords

Parkinson disease; twin; concordance; prevalence; family history

1. Introduction

Despite the discovery of several Parkinson disease (PD) genes and environmental risk or protective factors [4], the etiology of PD remains poorly understood. Twin and family studies are valuable tools for evaluating potential risk factors of multi-factorial diseases. By comparing disease concordance rates between monozygotic and dizygotic twins, the relative importance of genetic and environmental factors in disease etiology can be studied. In evaluating specific environmental exposures, studies of monozygotic twin pairs discordant for the disease reduce confounding by genetic factors [16].

One twin study of male twins found evidence for a genetic component in early onset PD, but for environmental influences in late onset PD [27]. The aims of the present study were a) to investigate the relative importance of genetic and environmental factors in PD using the Swedish Twin Registry (STR), a large population-based twin cohort including both men and women; b) to explore a wide range of environmental risk factors and their potential role in PD, as well as the role of gene by environment interactions. Through population-wide screening of all Swedish twins aged 50 years or older, we set out to ascertain all cases of PD. This report sets the foundation for a series of studies based on this sample. We describe the methods used, the ascertainment process, prevalence, and concordance rates for PD, prevalence of cognitive impairment and reported family history among PD cases.

2. Methods

2.1 Study Population - The Swedish Twin Registry

The STR contains information on over 70,000 twin pairs born between 1886 and 2000 in all of Sweden [14]. The study population, 49,814 individuals, included all twins eligible for the Screening Across the Lifespan Twin study (SALT, see below) who were at least 50 years of age by the date of their interview, or if no interview was completed, the date of their letter notifying them of SALT was sent.

Twins in the study population were ascertained for PD in three phases. See Figure 1 for an overview of the study design. In the first phase, twins were screened for PD and PD symptoms by telephone as part of SALT. The purpose of this screening was to be inclusive rather than specific. Twins were tentatively regarded as PD cases if they or their proxy responded “yes” when asked whether they had ever been diagnosed with PD. Twins who responded “no” were regarded as possible suspects if they met any of the following criteria: a) positive for one of the two symptom algorithms (see below); b) reported the use of anti-parkinsonian medication (excluding those taking l-dopa for restless legs); or c) had a PD diagnosis in the Swedish National Inpatient Discharge Register (IDR). In the second phase, we sought to exclude twins from further follow-up who were PD suspects due to symptoms related to diseases other than PD. The third phase involved clinical evaluations of twins who were still suspects after the second screening, twins with self- or proxy-reported PD from SALT, twins with suspected PD from a previous dementia study, and a sample of co-twins.

2.2 Phase I - Screening Across the Lifespan Twin Study

Between 1998 and 2002, the STR contacted all living twins born 1958 or earlier using computer-assisted telephone interviews [14]. The interview included a checklist of common

diseases including PD. There was also a series of questions about a variety of PD symptoms and the use of anti-parkinson medication (originally developed by Tanner et al [26]) that was administered to individuals aged 50 or older.

PD symptoms included trouble arising from a chair, small handwriting, poor balance, feet getting stuck to the floor, little facial expression, shaking arms or legs, difficulty buttoning buttons, shuffling feet or taking tiny steps when walking, soft voice and slow movements. If the twin said yes to two symptoms or more, the twin was asked age of onset and whether onset was gradual or sudden. If it was not possible to talk to the twin (for example due to cognitive impairment or hearing problems), interviewers requested to speak with a proxy. In these cases, questions about a previous PD diagnosis and anti-parkinson medications were included, but questions about PD symptoms were omitted.

2.3 SALT Screening Algorithms

To identify twins who exhibited early symptoms of PD but had not yet received a PD diagnosis, we constructed two algorithms to evaluate responses to the PD symptom questions in SALT. The first algorithm, referred to as the parkinsonian algorithm, was designed to map on to diagnostic criteria for PD based on results from previous validation studies of screening questions [5,20–22,26]. Twins were considered positive if they endorsed shaking arms or legs plus one of the following four symptoms: Small handwriting, feet stuck to the floor, difficulty buttoning buttons and soft voice. The second algorithm, referred to as the bradykinesia algorithm, was not based on previous validation studies. Twins were considered positive if they did not endorse shaking arms or legs but did endorse three of the four symptoms mentioned above. Those who reported sudden onset of symptoms, multiple sclerosis, polio as a child, or neuroleptic drug use were excluded prior to the second phase.

2.4 Zygosity Determination

Determination of zygosity was based on questions about childhood resemblance in the questionnaires given at the time of registry compilation or in SALT. The procedure was validated with 13 microsatellite markers and found to be 99% accurate [14].

2.5 Swedish National Inpatient Discharge Register

The IDR covers all public inpatient care (most of the healthcare) in Sweden between 1987 and 2002 [19]. Primary and additional diagnoses are coded according to the International Classification of Diseases (ICD) [30]. To define cases of PD, the ICD codes 342, 332.0, and G20 were used for ICD8, ICD9, and ICD10, respectively. PD cases were identified by record linkage with the STR through the ten-digit national registration number assigned to all inhabitants of Sweden.

2.6 Phase II - Second Screening through HARMONY

During SALT, all twins over the age of 65 were also screened for dementia using a telephone cognitive mental status evaluation [11,12] in combination with a proxy interview using the Blessed Dementia Rating Scale (BDRS) [3], to assess how much cognitive problems interfered with daily functioning. These were combined into a scale with scores ranging from 0 (cognitively intact) to 3 (suspected of dementia). Twins who scored 3 on cognitive screening and their co-twins were worked up clinically through the HARMONY study, including a complete somatic and neurological examination, neuropsychological testing, and proxy interviews [10]. Dementia diagnoses were assigned using DSM-IV [2]. In total 1,557 twins were worked up with regard to dementia diagnoses. From the neurological examinations included in these assessments, we identified twins with suspected PD, who were referred for a PD diagnostic workup in the present study.

2.7 Phase II - Parkinson Disease Second Screening

Beginning in May of 2002, PD suspects from SALT were contacted again for a second screening interview. PD suspects by SALT who participated in HARMONY were not contacted, as participation in the HARMONY workup was considered to serve an equivalent purpose. The purpose of this interview was to exclude PD suspects from further follow-up who reported symptoms and PD medication due to diseases other than PD. We did not try to discriminate between PD and parkinsonism due to other diseases. A similar interview was performed in the Tanner study [27].

The interview, modeled after the Parkinson's Patient Motor Self-report Scale [29], included questions identical to SALT, as well as additional questions about PD symptoms and diagnosis, other diseases, and medications. Responses were scored to determine whether the twin screened positive or negative for each cardinal sign of PD (resting tremor and bradykinesia). Twins who were positive for the parkinsonian algorithm in SALT were excluded from further follow-up if they screened negative for resting tremor, or if they screened positive for resting tremor and negative for bradykinesia. Twins who were positive for the bradykinesia algorithm in SALT were excluded from further follow-up if they screened negative for bradykinesia in phase II. For each cardinal symptom endorsed, follow-up questions asked whether the symptom was reported for reasons clearly unrelated to parkinsonism, in which case the symptom was considered negative for screening purposes. Twins taking regular neuroleptic treatment prior to the onset of symptoms were also excluded. To be excluded, the twin had to say "no" to the questions about PD diagnosis and anti-parkinson medication. For suspects not excluded by the exclusion algorithm, answers to the second screening interview were reviewed by the study physician (MF) for any misunderstandings or other obvious reasons for reporting parkinsonian symptoms other than PD, for example hydrocephalus or previous brain trauma. In the latter cases, information from medical records was also available.

In the second screening interview, we also contacted co-twins of twins with suspected PD or self-reported PD who participated in the second screening, so that twin pairs would have equivalent screening.

2.8 Phase III - Diagnostic Workup

2.8.1 Clinical Workup—Twins with self- or proxy-reported PD in SALT, PD suspicion by HARMONY, and twins still considered suspects after the PD second screening interview were referred for a clinical workup. In addition, the first 102 co-twins were also referred for a clinical workup. For most of the PD suspects and co-twins, the clinical workup consisted of an in-person somatic examination in addition to medical record review; for most of the twins with self- or proxy-reported PD, the clinical workup was based on medical record review alone plus telephone interview.

The in-person clinical workup consisted of a home visit by the study physician (MF) for a complete neurological examination, general somatic and psychiatric examinations, an inventory of current medications, and medical history. Average duration of a visit was two hours. The Unified Parkinson's Disease Rating Scale [9] was used to evaluate parkinsonian signs and symptoms. The examination was documented on video according to a standardized protocol. Twins with suspected memory problems were evaluated by neuropsychological testing and proxy interviews.

For the twins with self- or proxy-reported PD in SALT or PD suspicion by HARMONY, the clinical workup consisted of a review of all relevant medical records. A nurse also performed a telephone interview with these twins, including detailed questions about symptom onset and manifestation of the disease. For twins who died between screening and clinical workup, a

modified interview was performed with a relative. Twins with insufficient information in medical records to assign a diagnosis, or with a record of PD diagnosis only by a general practitioner, were visited by the study physician (MF) according to the same protocol as the PD suspects.

2.8.2 Assignment of Parkinson Disease Diagnoses—Diagnoses based on somatic exams were assigned by the study physician (MF), together with a movement disorder specialist (HW). Another movement disorder specialist (GP) independently assigned diagnoses based on reviewing the videotaped examination and the notes made during the somatic exam. Cases in which there was disagreement were reviewed by a third movement disorder specialist (ML). Final consensus diagnoses were all agreed upon by two movement disorder specialists (GP and ML). Diagnoses based on medical records were assigned by the study physician (MF), together with one movement disorder specialist (HW). NINDS diagnostic criteria for PD [13] were used.

2.9 Risk Factor Assessment and Collection of Blood Samples

The initial SALT interview included questions about occupation, diet, medications, smoking, and alcohol consumption. Additional information on potential risk or protective factors was collected at two points in the present study. First, twins and their co-twins were, in the second interview, asked a series of detailed questions about environmental risk factors, such as places they have lived, occupations, specific exposures related to both occupation and leisure activities (for example pesticides and solvents), head injuries, stress, and medical risk factors such as medication use. Twins who were not called for a PD second screening interview due to their participation in HARMONY were asked the risk factor questions during the HARMONY interview. Wherever possible a proxy was interviewed if the twin could not talk on the phone.

Second, all twins who had a further diagnostic workup and their co-twins were called by one of three trained nurses for additional risk factor information primarily related to occupational exposures. For different sets of occupations, question modules were constructed that covered the common exposures for those specific occupations. In the same interview, nurses collected family history of first degree relatives. A questionnaire regarding food habits and personality traits was mailed to the twins. The nurses also organized the collection of blood samples.

2.10 Statistical Analysis

All statistical procedures were performed using SAS, version 9.1 [24]. Logistic regression was used to compare characteristics between participants and dropouts in the SALT screening interview, the PD second screening interview, and the clinical workup. Results are presented showing the odds ratios (ORs) and 95% confidence intervals (CIs). Age was categorized into five ten-year intervals (50–59, 60–69, and 90+) based on age at SALT interview.

To estimate the prevalence of PD in the study population, we adjusted first for non-participation in the SALT screening interview, and second for non-participation in the PD second screening interview and in the clinical workup. To adjust for non-participation in SALT screening, we used information from the IDR. We first calculated the response rate in SALT for twins with a PD diagnosis in the IDR, and assuming the same response rate among self-report cases, we estimated the number of expected cases among non-respondents in SALT. For the other categories of PD suspicion, we assumed the same response rate as for the study population in general. To adjust for non-participation in the PD second screening and in the clinical workup, the number of twins given a PD diagnosis by diagnostic workup over the total number of twins with a diagnostic workup was applied to the total number of twins within each category of suspicion. As only one of the four PD suspects identified in HARMONY and diagnosed with PD participated in SALT screening, suspects identified by HARMONY were excluded from

the prevalence count to avoid over-adjusting. To deal with the fact that the sample contained related individuals, we used a bootstrapping technique [6] with a resampling process iterated 3,000 times to calculate 95% CIs for the prevalence rate, as well as 95% CIs for the OR comparing the unadjusted prevalence rate by sex and zygosity. Base populations were all twins who participated in SALT (N=36,197) for the unadjusted prevalence rate and the study population (N=49,814) for the adjusted prevalence rate.

3. Results

3.1 SALT Screening Dropout Analysis

The study population and participation in the SALT screening interview are described in Table 1. Differences between participants and non-participants in SALT have been reported earlier [8,10]. Significant predictors of participation were age (although average age difference between participants and non-participants was less than 90 days) and being a monozygotic twin. Among twins above 65 years, men were more likely to participate than women, but among twins between 42 and 64 years, women were more likely to participate than men [8,10]. Among twins above 65 years, with increasing age, pairs were less likely to be complete and monozygotic pairs were more likely to be complete than same-sexed dizygotic and opposite-sexed twins [10]. The principal reason that one twin completed SALT screening and their co-twin did not was that the co-twin had died before SALT began or died during the SALT study. Twins with a PD diagnosis documented in the IDR before the end of 2002 were less likely to participate in SALT (OR 0.47, 95% CI 0.36, 0.62).

3.2 Parkinson Disease Second Screening Dropout Analysis

Numbers of PD suspects at the end of SALT by sex and age group as well as participation in the second screening interview are shown in Table 2. See also Figure 1. There were no significant differences by age group, sex, zygosity, PD diagnosis in the IDR, or mode of suspect identification between twins who completed the second screening and twins who did not. Twins not contacted for the second screening (due to death before screening began or administrative error) did not differ by sex, zygosity, or PD in the IDR from twins who were contacted. Twins not contacted for the second screening interview due to administrative error were on average 13 years younger than twins who were contacted ($p < 0.0001$).

3.3 Diagnostic Workup Drop out Analysis

For PD suspects referred for workup (Figure 1), there were no differences by sex or zygosity between participants and non-participants. PD suspects above 80 years were less likely to participate than 50- to 60-year-olds (OR 0.16, 95% CI 0.03, 0.79), but comparing 60- to 70-year-olds and 70- to 80-year-olds versus 50- to 60- year-olds, there were no significant differences.

3.4 Clinical Diagnosis Results

Diagnoses were assigned for 420 twins by the study physician (MF) and the first movement disorder specialist (HW), 225 based on somatic exams (128 probands and 97 co-twins) and 195 based on medical records (190 probands and 5 co-twins). The second movement disorder specialist (GP) independently assigned diagnoses for the 222 twins whose somatic exam was documented on video, and an additional two twins without a video.

When we examined agreement between physicians, in 47 of the 224 cases, there was disagreement between the initial and second diagnoses as to whether PD was present, but disagreement on possible versus probable PD only in two cases. For the 47 cases, a third diagnosis was independently assigned by movement disorder specialist ML, discussed with

GP, and determined to be the consensus diagnosis. In 31 of these 47 cases, the consensus diagnosis agreed with the original diagnosis. Thus, in only 16 of 224 cases did the initial diagnosis change when the final consensus diagnosis was assigned. We identified 99 twins with probable PD and 33 twins with possible PD (Table 3). Mean age of onset was 64.3 ± 10.6 years (range: 39 – 90) for probable PD and 71.7 ± 8.5 years (range: 44 – 88) for possible PD. In total 62 twins were given a parkinsonism diagnosis.

Of those with a diagnostic workup, the proportion assigned a probable or possible PD diagnosis was highest for self- or proxy-report cases (70.1%), whereas 25.0% of cases with a PD diagnosis in the IDR but no self-reported diagnosis and under 5% of those screened positive by either the parkinsonism or bradykinesia algorithm were assigned a PD diagnosis. Six individuals diagnosed as PD (two with probable PD and four with possible PD) were co-twins who screened negative for PD and received a clinical evaluation as a co-twin. Of these six, however, age of onset for PD was after SALT screening for three.

3.5 Prevalence of Parkinson Disease

The overall unadjusted estimated prevalence rate of PD was 345 per 100,000 individuals (95% CI 285, 409 per 100,000); 415 per 100,000 individuals in men (95% CI 325, 511 per 100,000), and 286 per 100,000 individuals in women (95% CI 210, 363 per 100,000). The overall adjusted estimated prevalence rate of PD was 496 per 100,000 individuals; 547 per 100,000 individuals in men, and 436 per 100,000 individuals in women (Figure 2). The sex difference was statistically significant (OR 1.45, 95% CI 1.01, 2.13 for men versus women). Prevalence was slightly lower in monozygotic twins than in same-sexed dizygotic and opposite-sexed twins, but the difference was not statistically significant (OR 0.79, 95% CI 0.46, 1.22).

3.6 Twin Pairs Concordant for Parkinson Disease

Only three pairs were concordant for PD; one male monozygotic pair and two female dizygotic pairs. Mean difference in age of onset of PD between the twins in these pairs was seven years.

3.7 Family History of Parkinsonism

Family history information about reported PD, suspicion of PD, or tremor in first degree relatives was available for 113 PD cases. Among PD cases in discordant pairs, 5.6% reported a first degree relative with a PD diagnosis, 23.4% reported either a PD diagnosis or suspicion of PD among first degree relatives, and 38.3% reported either a PD diagnosis, suspicion of PD, or any kind of tremor among first degree relatives. The results were similar in men and women. Two of the three twin pairs concordant for PD had a first degree relative (other than the co-twin) with a PD diagnosis, and the other twin pair had a first degree relative with tremor.

3.8 Cognitive Impairment among PD Cases

Figure 3 shows cognitive status as a result of the SALT screening for the twins 65 years or older with a PD diagnosis. Among these 108 twins, 20 performed poorly (scored 2) on the cognitive screening test in SALT, and 23 met criteria for suspicion of dementia (scored 3). Rate of diagnosed dementia was 15.7%. An additional 5.6% were diagnosed with questionable dementia.

4. Discussion

We have described a new study of PD based on a large population-based sample of Swedish twins. A strength of our study is that we assessed a population-based cohort that is spread over all of Sweden. The first screening was designed to be as inclusive as possible. The main predictor of non-participation was record of a PD diagnosis in the IDR. Since having a PD

diagnosis in the IDR probably is related to either severe disease or substantial co-morbidity, severe PD cases may be under-represented in our sample. However, through the overlap with the HARMONY study, we had an alternative method to identify PD cases with dementia. Agreement between diagnosticians was high. Of 102 initially screened negative co-twins with a diagnostic workup, three were diagnosed with PD with age of onset for parkinsonian symptoms before the screening interview, representing a low false negative rate.

The prevalence rate for PD in this study, 496 per 100,000 individuals, was comparable to many previous studies, although others typically do not adjust for non-participation. We were able to adjust our prevalence rate for non-participation using information from the IDR. One review including 34 European PD prevalence studies reported overall estimates between 108 and 257 per 100,000 individuals for “high-quality” studies [31], although there was a large variation. Some studies found a higher prevalence in men than in women as we did, but other studies could not confirm this finding. Studies employing door-to-door surveys reported higher prevalence rates, 257 to 1500 per 100,000 individuals, compared to studies using other methods of ascertainment [31]. This range is in line with our overall estimate. Studies from other parts of the world (USA, China and Argentina) have reported prevalence rates between 107 and 867 per 100,000 individuals [17,18,27,28].

Our sample of twins above the age of 65 is identical to the sample used in a previous dementia study [10] and we therefore assessed the presence of dementia among PD patients in this age group. A review including 12 prevalence studies of dementia in PD reported an average proportion of dementia in PD cases of 24.5% [1]. Door-to-door surveys reported a lower proportion (16%) compared to studies using other methods of ascertainment [1]. Our results of 15.7% with dementia and another 5.6% with questionable dementia are thus comparable to the literature.

The low numbers of twin pairs concordant for PD in our study support previous results [27] and indicate that environmental factors are most important in the etiology of PD. Our frequency of first degree relatives with a PD diagnosis among twin pairs discordant for PD, 5.6%, is in the same range as other population-based family studies [7,15,23,25]. Although the difference was sometimes small [23], the frequency of first degree relatives with a PD diagnosis was higher in PD patients than in controls in all studies. A possible explanation for the familiarity of PD despite the low number of twin pairs concordant for PD is shared familial environmental effects. However, together with the relatively large number of PD genes, gene by environment interaction is suggested.

Limitations of the study include imperfect response rates and loss to follow-up primarily due to the time lag between SALT and the second screening. Quality of diagnoses may differ depending on whether a somatic examination was performed by us or not; lack of information in medical records may make the diagnostician less inclined to assign a PD diagnosis. Further, the study would have benefited from a national outpatient discharge registry.

In conclusion, through population-wide screening of almost 50,000 twins all over Sweden followed by detailed diagnostic workups, we have identified a sample of twins with PD. The prevalence rate for PD in this population was comparable to the literature. We identified only three twin pairs concordant for PD, indicating that environmental factors are most important for disease etiology. Our sample provides the basis for future studies regarding environmental causes and gene by environment interactions in PD.

Acknowledgements

The study was supported by grants from the National Institutes of Health; ES10758 and AG 08724, the Swedish Medical Research Council and the Swedish Medical Society. The authors thank the project nurses Karin Dellenvall, Marie Hallin, and Gunilla Hedlund for help with data collection, and Dr Alexander Ploner for statistical advice.

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Figure 1. Overview of study design

1. Participation rate 72.7%. N=36,033 individuals responded to the specific questions about PD; n=35,031 (97.2%) themselves and n=1,002 (2.8%) through a proxy.
2. Of the n=577 PD suspects by SALT not worked up in the dementia study, n=68 were dead or were not willing to be contacted again by the STR, and n=57 were not contacted due to administrative error.
3. Participation rate 77.2%.
4. N=182 directly by the exclusion algorithm and n=21 after review of answers by the study physician.
5. N=143 co-twins of twins with suspected PD not suspected themselves plus n=129 co-twins not suspected themselves of twins with self- or proxy-reported PD who participated in the second screening interview, resulted in n=272 co-twins whom we wanted to contact. Of these, n=19 were already included in the dementia study, n=61 were dead, and n=24 refused SALT and were therefore not contacted again.
6. Participation rate 79.8%.
7. The dementia study is referred to as HARMONY, which is an acronym for the Swedish words “health” (H), “genes” (ARv), “environment” (M), “And” (O) and “new” (NY).

8. N=10 participated themselves in the SALT interview, n=14 were interviewed through a proxy, and n=10 were not possible to interview but a proxy indicated that the twin had cognitive dysfunction.
9. N=146 not excluded by second screening telephone interview; n=7 not excluded after dementia workup.
10. N=121 by somatic examination and n=15 by medical records. N=11 refused, n=7 died after the second screening interview, and n=1 was not worked up due to logistical difficulties.
11. N=97 by somatic examination and n=5 by medical records.
12. N=173 by medical records and n=9 by somatic examination in addition to medical records.

In the remaining n=6 cases, a diagnosis could not be assigned due to insufficient information (for example, medical records could not be obtained).

Prevalence of PD, per 100,000 individuals

Figure 2. Unadjusted and adjusted prevalence of PD by age group

Point estimates for the unadjusted prevalence were 69 per 100,000 individuals (95% CI 34, 109 per 100,000) for the age group 50–59 years, 352 per 100,000 (95% CI 233, 476 per 100,000) for the age group 60–69, 802 per 100,000 (95% CI 571, 1033 per 100,000) for the age group 70–79, and 1146 per 100,000 (95% CI 722, 1614 per 100,000) for the age group 80–89. There were no PD cases in the 90+ age group. Point estimates for the adjusted prevalence were 99 per 100,000 individuals for the age group 50–59 years, 506 per 100,000 for the age group 60–69, 1063 per 100,000 for the age group 70–79, and 1508 per 100,000 for the age group 80–89.

Figure 3. Cognitive status of PD cases 65 years or older at SALT screening

Score 0 to 3 refers to the scale based on the cognitive mental status evaluation and the proxy interview.

Table 1

Participation in SALT by sex, zygosity, and age group.

	Study population N	Participants N (%) ¹⁾	Non-participants					
			Refused N (%)	Not possible to interview N (%)	Not reachable N (%)	Died between selection and screening N (%)	Not contacted N (%)	In previous aging study N (%)
All twins	49814	36197 (72.7)	8086 (16.2)	846 (1.7)	4151 (8.3)	406 (0.8)	60 (0.1)	68 (0.1)
Sex								
Men	22948	16638 (72.5)	3391 (14.8)	333 (1.5)	2321 (10.1)	221 (1.0)	26 (0.1)	18 (0.08)
Women	26866	19559 (72.8)	4695 (17.5)	513 (1.9)	1830 (6.8)	185 (0.7)	34 (0.1)	50 (0.2)
Zygosity ²⁾								
MZ	10861	8769 (80.7)	1240 (11.4)	189 (1.7)	554 (5.1)	80 (0.7)	7 (0.1)	22 (0.2)
DZ	17560	13897 (79.1)	2191 (12.5)	342 (2.0)	921 (5.2)	157 (0.9)	8 (0.1)	44 (0.3)
OS	17413	12821 (73.6)	2761 (15.9)	209 (1.2)	1469 (8.4)	124 (0.7)	29 (0.2)	0 (0)
Unknown	3980	710 (17.8)	1894 (47.6)	106 (2.7)	1207 (30.3)	45 (1.1)	16 (0.4)	2 (0.1)
Age group								
50–59 years	23035	17457 (75.8)	2830 (12.3)	84 (0.4)	2510 (10.9)	65 (0.3)	60 (0.3)	29 (0.1)
60–69 years	13013	9668 (74.3)	2257 (17.3)	101 (0.8)	932 (7.2)	53 (0.4)	0 (0)	2 (0.02)
70–79 years	9571	6485 (67.8)	2182 (22.8)	257 (2.7)	517 (5.4)	113 (1.2)	0 (0)	17 (0.2)
80–89 years	3762	2355 (62.6)	759 (20.2)	310 (8.2)	176 (4.7)	143 (3.8)	0 (0)	19 (0.5)

	Study population N	Participants N (%) ¹⁾	Non-participants					
			Refused N (%)	Not possible to interview N (%)	Not reachable N (%)	Died between selection and screening N (%)	Not contacted N (%)	In previous aging study N (%)
90+ years	433	232 (53.6)	58 (13.4)	94 (21.7)	16 (3.7)	32 (7.4)	0 (0)	1 (0.23)

¹⁾ Percentages were calculated as the proportion of the study population for each category (the sum across the row)

²⁾ MZ = monozygotic twins, DZ = same-sexed dizygotic twins, OS = opposite-sexed twins

Table 2
Twins with suspected PD at the end of SALT and participation in PD second screening, by mode of suspicion.

	Self- or proxy-reported PD diagnosis N	Parkinsonian algorithm ¹⁾ N	Bradykinesia algorithm ¹⁾ N	PD medications but no reported diagnosis N	Inpatient Discharge Register PD diagnosis before SALT ²⁾ but no reported diagnosis N	PD symptoms identified by HARMONY workup N
All twins	154 ³⁾	448	111	74 ⁴⁾ 5)	4	34
Participated in second screening interview		249	57	41	2	
Excluded as a suspect		(138)	(28)	(36)	(1)	
Participated in HARMONY		44	14	1	1	
Excluded as a suspect		(40)	(12)	(1)	(0)	
Non-Participation						
Refused		42	13	7	1 ⁶⁾	
Not possible to interview		15	2	0	0	
Not reachable		14	4	5 ⁷⁾	0	
Not contacted ⁸⁾		49	14	5	0	
Administrative error		35	7	15	0	
Sex						
Men	86	214	59	27	2	15

	Self- or proxy-reported PD diagnosis N	Parkinsonian algorithm ¹⁾ N	Bradykinesia algorithm ¹⁾ N	PD medications but no reported diagnosis N	Inpatient Discharge Register PD diagnosis before SALT ²⁾ but no reported diagnosis N	PD symptoms identified by HARMONY workup N
Women	68	234	52	47	2	19
Age group						
50–59 years	14	128	26	33	0	0
60–69 years	40	93	20	27	1	1
70–79 years	61	135	37	10	1	13
80–89 years	37	86	26	4	2	19
90+ years	2	6	2	0	0	1

¹⁾Twins who responded to the SALT pilot interview were not asked the question about a soft voice, and therefore, their algorithms were calculated with one less symptom

²⁾PD diagnosis in the IDR before March 31st 1998

³⁾N=112 twins with self-reported PD and n=42 twins with proxy-reported PD

⁴⁾One twin in this category was also identified as a suspect by the bradykinesia algorithm

⁵⁾An additional 16 twins were excluded since they reported taking L-dopa for restless legs

⁶⁾A PD diagnostic workup was completed although the twin did not participate in the second screening

⁷⁾For one twin in this category, a PD diagnostic workup was completed although the twin did not participate in the second screening

⁸⁾Not contacted either due to death before or during the screening period, or a previous request in SALT to not be contacted again by the STR

Table 3

Clinical diagnoses for study population.

Diagnosis	N
<i>PD</i>	
Possible PD	99
Probable PD	33
<i>Parkinsonism</i>	
PSP ¹⁾	6
MSA ²⁾	3
Cerebrovascular parkinsonism	32
Parkinsonism due to neuroleptics	11
Parkinsonism in dementia other than LBD	5
Parkinsonism of unknown cause	5
<i>Other neurological diseases</i>	
Lewy body dementia	11
Cerebellar disease	6
Essential tremor	52
Other ³⁾	6
<i>No neurological disease</i>	151
Total	420

¹⁾ PSP = Progressive supranuclear palsy

²⁾ MSA = Multiple system atrophy

³⁾ Includes restless legs, hereditary dystonia, polyneuropathy, tics