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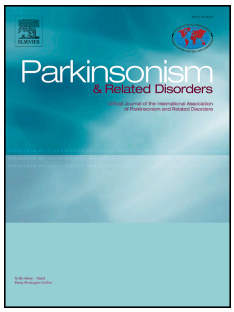

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Systematic review and meta-analysis of hydrocarbon exposure and the risk of Parkinson's disease

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Key Words: Parkinson's disease; hydrocarbon, occupational exposure; case-control

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Abstract

Background There is no consensus on the association between exposure to hydrocarbons and the risk of Parkinson's disease (PD). We conducted a systematic review and meta-analysis to summarise the epidemiological evidence and included a new large case-control study.

Methods Data were extracted following a predefined protocol. Risk estimates regarding the association between hydrocarbon exposure and PD were consolidated to produce a summary odds ratio (OR), 95% confidence intervals (CI), and p-value. In our case-control study, 1463 PD patients and 685 controls were recruited from clinical trials and completed a structured questionnaire describing their previous working exposure to hydrocarbons and other demographic measures. The association between exposure to hydrocarbons and risk of PD was evaluated using logistic regression.

Results The systematic search identified 13 case-control studies matching the inclusion criteria. The meta-analysis included 3020 PD cases and 6494 controls. The summary OR was 1.32 (95% CI 1.08-1.62, p=0.006) for hydrocarbon exposure (ever versus never). In the PD GEN study, occupational exposure to hydrocarbons significantly increased the risk of PD (OR=1.61; 95% CI 1.10-2.36, p=0.014), and risk dose-dependently increased for subjects exposed greater than 10 years compared to subjects never exposed (OR=2.19; 95% CI 1.13-4.26, p=0.021). The addition of PD GEN data increased the total numbers to 4483 PD cases and 7179 controls and strengthened the significant association (summary OR=1.36; 95% CI 1.13-1.63, p=0.001).

Conclusions This systematic review supports a positive association between hydrocarbon exposure and PD. Data from prospective studies is required to reinforce the relationship between hydrocarbon exposure and PD.

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Introduction

Parkinson's disease (PD) is the second most common neurodegenerative condition after Alzheimer's disease, affecting over 100,000 people in the United Kingdom (UK) and over one million people in the United States (US) [1]. The prevalence in the population is 0.3%, and rises exponentially with age reaching 4% in the highest age groups. As the population ages, PD is predicted to cause a major burden on both individuals and societies. The aetiology of PD remains largely unknown, although there is evidence that both genetic and environmental factors contribute [2]. Despite extensive epidemiological studies investigating lifestyle, environmental and occupational risk factors, only a small number of factors have shown a consistent association [3;4].

There is some limited data describing an association between hydrocarbon exposure and PD. Hydrocarbons are present in a broad range of products, including petroleum and other fuels, solvents, paints, glues and cleaning products [5]. The current systematic review and meta-analysis evaluated the relationship between hydrocarbon exposure and the risk of PD and included a new case-control study, PD GEN, which contained the largest number of PD patients to date.

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Methods

Systematic review

We undertook a systematic search of the published literature to identify observational studies that reported exposure to hydrocarbons and PD, in accordance with the MOOSE guidelines. The broad search terms listed were combined with an observational studies filter as designed by the Scottish Intercollegiate Guidelines Network: (Parkinson's disease OR Parkinson) AND (Hydrocarbon OR Hydrocarbons OR Polycyclic Hydrocarbons, aromatic OR Solvent OR Hexane OR Occupational Exposure). We searched the Medline and Embase bibliographic databases from 1946 and 1947 to July 2012, respectively, and screened the reference lists of retrieved articles for further relevant papers.

Studies were included if they met the following eligibility criteria: PD as the outcome of interest, an appropriate confirmation of diagnosis (e.g. neurologist or PD inclusion criteria or medical records), and present a risk estimate. Chlorinated hydrocarbon pesticides were excluded from the review. Double data extraction was performed to identify information on the individual studies and participant characteristics. Hydrocarbon exposure data was recorded as ever versus never, for use in the meta-analysis. Additional information was recorded on the length of exposure and specific hydrocarbon agents.

The statistical software RevMan (version 5.1; Cochrane Collaboration 2011) was used to analyse the data. The adjusted OR (if adjustment was performed), for each study was combined using a generic inverse variance method to produce a summary OR and 95% CI [6]. We used a random-effects model and measured the heterogeneity across

studies using chi-squared test to calculate the p value and I^2 statistic [6]. The I^2 statistic is a measure of the percentage of total variation across studies that is due to heterogeneity beyond chance. To assess potential publication bias we constructed a funnel plot and performed an Egger's test. The analysis was first performed with the studies identified in Table 1, and then subsequently including our study, PD GEN, as described below. We also stratified by whether non-occupational (i.e studies which measured exposure through recreation/hobby) exposure was recorded in the exposed group, which allowed us to assess potential differences in intenisty of the hydrocarbon exposure. It is important to note, during data extraction two studies presented separate occupational and non-occupational risk estimates [7;8]. Thus for these two studies, we used these separate odds ratios in the stratified meta-analyses (as these studies did not produce an overall risk estimate); and used the occupational only risk estimate in the overall meta-analysis as it contained the greatest number of exposed subjects. Additional data from our study is described as follows.

Subjects

The PD GEN database was created at the Birmingham Clinical Trials Unit and the Molecular Neurology Group, School of Clinical and Experimental Medicine, University of Birmingham. Recruitment began in June 2002 with patients and carers enrolled in three UK wide, large pragmatic randomised control trials (RCTs): PD MED, PD REHAB and PD SURG. All patients and carers provided written informed consent and the study was approved by the Multicentre Research and Ethics Committee (MREC/00/7/56a). Further trial information is available at:

http://www.birmingham.ac.uk/research/activity/mds/trials/bctu/trials/index.aspx

Patients had varying severity and disease duration, thus giving a large representative sample of PD patients. All patients enrolled into PD GEN have been diagnosed with PD by a neurologist or geriatrician using the UK Parkinson's Disease Society Brain Bank diagnostic criteria for idiopathic PD [9]. By January 2013, a total of 1463 PD patients had been recruited to the study. The carer control group consisted of 685 subjects who were predominantly spouses but included some friends. Blood relatives were not included. Participants were excluded if they were incapable of giving written informed consent.

Data collection

Data from the PD patients and carer controls were collected using a structured self-reported questionnaire when they were enrolled in PD GEN, along with a blood sample for genetic analyses. The questionnaire requested information on demographic characteristics, smoking status, and daily caffeine intake (including coffee and tea consumption). Participants were also asked to recall their medical and family history (including PD family history up to second degree relatives) and working exposure during employment to hydrocarbons. More detailed questions ascertained the years of exposure in employment and an open ended question enquiring about specific hydrocarbon agents. To minimise recall and response bias when answering the questionnaire, participants were not informed of any potential research hypothesis.

Data analysis

The demographic characteristics were compared between PD cases and controls using a Pearson chi-square test for categorical variables and a two-sample t-test for continuous variables. Logistic regression models were used to evaluate the association between exposure to hydrocarbons and risk of PD. The odds ratios (OR), 95% confidence intervals (CIs), p-values and p for trend values for three hierarchical models are presented; crude; adjusting for age and sex; and additionally adjusting for cigarette smoking, caffeine intake, pesticide exposure and PD family history. Analyses assessed exposure to hydrocarbons (ever versus never exposed), with never exposed used as the reference group. Separate analyses comparing duration of exposure to hydrocarbons were also conducted, comparing 1-9 years of exposure versus never exposed and >10 years of exposure versus never exposed. The associations between specific hydrocarbon agents (trichloroethylene and carbon tetrachloride), groups of hydrocarbon agents (pure hydrocarbons and chlorinated hydrocarbons) and exposure to paints were determined in an exploratory manner using the aforementioned logistic regression analyses, recognising that such analyses would likely be under powered. All tests were 2-sided and p-values of 0.05 or less were considered as statistically significant. Analyses were performed using SPSS statistical software version 20.

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Results

Figure 1 shows the process of study selection for the systematic review (PRISMA statement). 743 abstracts were screened for relevance, of which 13 eligible studies were included in the meta-analysis. The included studies comprised of a total of 3020 PD patients and 6494 controls. Supplementary Table 1 shows the information on the individual studies and participant characteristics. Figure 2 presents a forest plot displaying the association between exposure to hydrocarbons and risk of PD; these results indicate that exposure to hydrocarbons is associated with a significantly increased risk of PD (OR 1.32; 95% CI 1.08-1.62, p=0.006). There was no significant between-study heterogeneity (I^2=28%; p=0.17).

Supplementary Table 2 shows the demographic characteristics of the PD patients and their carers from the PD GEN dataset. 1463 PD patients and 685 carer controls were recruited. The mean age of PD patients and controls were 75.2±9.4 and 73.1±9.7 years, respectively. Of the cases, 66.5% were male compared to only 25.4% males in the carer group, thus females were over represented in the carer group compared to the PD patient group. Analyses were adjusted for gender in order to adjust for the potential confounding effect of this variable. Additionally, sex-stratified analyses were also performed. The increased risk estimate in the males was similar to that of the combined group, although the effect size was of borderline significance OR=1.59 (CI 0.95-2.65, p=0.079). The increased effect size in the females was lower than that observed in the male subgroup OR=1.17 (CI 0.62-2.19, p=0.62). Associations between exposure to hydrocarbons and risk of PD are presented in Table 1. There was a significantly increased risk of PD in individuals who were exposed to hydrocarbons compared to

those who were not after adjustment for potential confounding factors (OR=1.61, 95% CI 1.10-2.36, p=0.014). The total years of exposure was also significantly and linearly associated with PD (p=0.013), as was exposure for greater than 10 years when compared to never exposed subjects (OR=2.19, 95% CI 1.13-4.26, p=0.021). The adjusted ORs for the individual hydrocarbon agents and occupational exposure to paints suggested an increased risk, but the risk estimates were not statistically significant.

Adding our data slightly modified the effect size of the meta-analysis, and narrowed the CIs due to increased sample size (summary OR 1.36; 95% CI 1.13-1.63, p=0.001 Figure 2). There was no significant heterogeneity between the studies (I^2=29%; p=0.15). There was limited evidence of publication bias (Supplementary Figure 1; Egger p-value=0.014), however, when we conducted a sensitivity analysis by removing the two anomalous studies with extremely large ORs, there was no significant publication bias (Egger p-value=0.14). Figure 3A presents 9 studies which considered occupational exposures only, which showed an increased risk (OR 1.49; 95% CI 1.22-1.82, p=0.001). Figure 3B presents 7 studies which considered non-occupational exposures in the exposed group which increased the summary OR further to 1.57 (95% CI 1.08-2.29, p=0.02).

Discussion

The meta-analysis of 13 studies indicated that hydrocarbon exposure was estimated to significantly increase the risk of PD by 32%. The observed associations between hydrocarbon exposure and PD risk varied from 1.01 to 9.51 across the 13 included studies [10;11]. Specifically, the PD GEN data indicate that exposure to hydrocarbons was significantly associated with a 61% increased risk of PD, which was consistent with the majority of effect sizes incorporated in the meta-analysis. Adding the PD GEN data in the overall meta-analysis of 14 studies slightly increased the overall risk estimate, indicating that hydrocarbon exposure increases the risk of PD by 36%. The studies included in the meta-analysis had differences in recording and reporting exposures, population groups, specific hydrocarbon agents as well as many studies involving few cases. Despite this, there was no significant heterogeneity in the overall meta-analysis (I^2=29%) between the risk estimates of the studies.

A similar positive association was shown when we stratified by occupational only and occupational and/or non-occupational (i.e. recreational/hobby-related) hydrocarbon exposures. Occupational only hydrocarbon exposure increased the risk of PD to 49% [7;8;11-16]. The risk estimate further increased when occupational and/or non-occupational exposure studies were also assessed [7;8;17-20], with a calculated 57% increased risk albeit with a wider CI. Interestingly, the two studies which presented separate risk estimates for occupational and non-occupational exposures also describe a larger risk estimate for recreational exposure to hydrocarbons through hobbies [7;8]. The increased risk shown in these studies, along with the meta-analysis could be a result of either increased mortality prior to the development of PD in occupationally-

exposed patients; or, a more plausible explanation would be that occupationally/highly-exposed individuals are provided with legally-required protective equipment that prevents inhalation of hydrocarbons and thus attenuates the increased risk of developing PD.

Previous reports of an association between PD and duration/intensity of hydrocarbon exposure or specific hydrocarbon agents have been varied. For example, in the largest overall case-control study to date, comprising 767 PD patients and 1989 controls, a stronger positive association was observed for low exposure when compared to high exposure [18]. In contrast the PD GEN study however, demonstrates a significant dose-trend relationship between increasing hydrocarbon exposure and PD risk. There are limited data on specific hydrocarbon agents, the associated risks of which have also varied. A recent twin study was the first to identify a significant positive association between trichloroethylene exposure and PD, although carbon tetrachloride and pure hydrocarbons including toluene, xylene, and N-hexane showed no association [13]. In other studies, toluene and naphtha have demonstrated a significant increased risk [11;19]. These studies have all used a small sample size with low exposure rates which would generate imprecise risk estimates. The PD GEN study measured specific exposure to chlorinated hydrocarbons, pure hydrocarbons or paints but no association was established, again possibly due to limited power.

The exact mechanism underlying hydrocarbon's potential neurotoxicity remains unclear, although experimental evidence has shown a range of harmful effects [21]. Using magnetic resonance spectroscopy, one study found parkinsonian patients with a high solvent exposure history had striatal neuronal damage compared to no damage in low

or zero exposed subjects [22]. The results suggested selective vulnerability of the basal ganglia to solvent damage which was corroborated by a dose relationship between exposure to solvents and neuronal damage [22]. In another study, 36 PD patients with history of occupational exposure to hydrocarbons were compared with 38 PD patients without exposure and healthy controls. Exposure to hydrocarbons significantly lowered striatal dopamine transporter binding measured by ^{123}I-ioflupane SPECT specifically in the putamen [23]. A combination of genetic and epidemiological risk factors may be required to induce neurodegeneration [24]. There is evidence of genetic polymorphisms influencing enzymes which metabolise foreign substances involved in hydrocarbon neurotoxicity [21]. Other studies have suggested the metabolism of hydrocarbon can produce toxic intermediates which induce mitochondrial dysfunction, through decreased complex 1 activity and increased oxidative stress [25]. For instance, trichloroethylene has been shown to reduce mitochondrial complex 1 activity in normal rats [26], so it may contribute to the risk of PD [27]. Further work is required to determine specific mechanisms of hydrocarbon toxicity in PD.

Systematic review methodology can provide the best overall estimate of the possible occupational exposure to hydrocarbons and risk of PD. However, the major limitation of the systematic review and meta-analysis was the clarity of the definition of hydrocarbon exposure of the included studies. There was a large variety of hydrocarbon agents included within the meta-analysis. The heterogeneity of hydrocarbons and products containing hydrocarbons may create a problem due to potential differences in toxicological properties. It may be that one specific hydrocarbon agent could be driving the observed positive association, and thus other agents could be attenuating the risk

estimate. As a consequence, we attempted to highlight broad categories of hydrocarbon agents to help prospective studies potentially identify a specific group or individual hydrocarbon agents that significantly increase the risk of PD. Nevertheless, the meta-analysis indicates overall hydrocarbon exposure is significantly associated with risk of PD [7;8;10-20;28]. Our case-control data are further limited by the use of spouse controls which led to differences in the prevalence of the sexes between cases and controls [29]. Additionally, the use of spouse controls may have also led to over-matching for common passive exposures. This would have reduced statistical power and underestimated effect size. The differences in prevalence of the sexes adds complexity to the interpretation of the data as professions that bring individuals into contact with hydrocarbons are more likely to be occupied by males. Sex stratified analyses revealed increased risk of PD with hydrocarbon exposure in both of the individual gender subgroups, however the risk estimates of the individual subgroups only reached borderline significance in the male subgroup due to the smaller number of individuals in the subgroup analyses. Overall the effect sizes observed in the combined sample (OR=1.61, 95% CI 1.10-2.36, p=0.014) and the male subgroup (OR=1.59, 95% CI 0.95-2.65, p=0.079) were of a similar magnitude, and were in line with those effect sizes observed in the review.

A second limitation is that, our study also included a disproportionate number of white participants and is thus not representative of the general UK population. Thirdly, although we adjusted for a number of potential confounders, others were not recorded including socioeconomic status, education, diet, and exposure to metals [3]. Lastly, an unavoidable limitation of all case-control studies is the lack of a temporal sequence to

infer causality and the introduction of recall-bias of the participants' exposure history. The retrospective nature of the questionnaire may have potentially introduced recall bias leading to an inaccurate exposure recording and attenuation of effect, which is particularly pertinent given the cognitive dysfunction seen in PD. We did not measure cognitive impairment upon entry to the study however, patients would not have been diagnosed with dementia as this was a criterion for exclusion from the study. In spite of these limitations, the results of the current PD GEN study are consistent with those of the meta-analysis, supporting the observed association between hydrocarbon exposure and PD risk.

In conclusion, there is growing epidemiological and experimental evidence of an association between hydrocarbon exposure and the risk of having PD. Our results corroborate previous hydrocarbon studies suggesting that hydrocarbons increase the risk of PD by around 36%. Data from large prospective cohort studies are required to further evaluate the association between hydrocarbon exposure and PD, expanding on these findings from case-control studies.

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Table 1- *Association between exposure to hydrocarbons, length of exposure and specific exposure and the risk of PD.*

	Cases		Controls				
	No.	**%**	**No.**	**%**	**OR (95% CI) unadjusted**	**OR (95% CI) Model 1**	**OR (95% CI) Model 2**
Hydrocarbon exposure							
Never	1231	84.5	636	93.1	1 (Ref)	1 (Ref)	1 (Ref)
Ever	225	15.5	47	6.9	2.59 (1.83-3.68) p=0.001	1.64 (1.12-2.38) p=0.01	1.61 (1.10-2.36) P=0.014
Years of Hydrocarbon exposure							
1-9	62	4.4	18	2.7	1.75 (1.01-3.04) p=0.045	1.32 (0.73-2.38) p=0.353	1.35 (0.75-2.44) p=0.323
>10	108	7.7	12	1.8	4.62 (2.46-8.69) p=0.001	2.28 (1.18-4.40) p=0.014	2.19 (1.13-4.26) p=0.021
p for trend					**<0.001**	**0.010**	**0.013**
Hydrocarbon							
Chlorinated hydrocarbons	40	3.1	9	1.4	2.31 (1.07-5.01) p=0.033	1.54 (0.67-3.49) p=0.303	1.54 (0.68-3.48) p=0.303
Trichloroethylene	13	1.0	3	0.5	3.34 (0.75-14.8) p=0.113	2.39 (0.50-11.3) p=0.272	2.47 (0.52-11.7) p=0.255
Carbon Tetrachloride	21	1.7	2	0.3	4.88 (1.13-21.0) p=0.033	3.46 (0.77-15.6) p=0.106	3.70 (0.81-16.8) p=0.09
Pure hydrocarbons	42	3.3	8	1.2	2.79 (1.24-6.29) p=0.013	1.63 (0.69-3.81) p=0.263	1.56 (0.66-3.70) p=0.309
Paints	57	4.4	12	1.9	2.52 (1.31-4.86) p=0.006	1.41 (0.71-2.81) p=0.33	1.45 (0.72-2.92) p=0.302
Other	60	4.6	15	2.3	2.44 (1.30-4.59) p=0.006	1.74 (0.89-3.38) p=0.104	1.67 (0.86-3.26) p=0.133

Model 1 adjusted for age and sex.
Model 2 additionally adjusted for cigarette smoking, caffeine intake, pesticide exposure, and PD family history.

Missing values= Hydrocarbon ever/never n= 9 (0.4%), Hydrocarbon years exposure n=72 (26.5%) - includes the participants that have indicated that they have been exposed but not stated how long for. Specific hydrocarbon agents n=50 missing (18.7%).
Note some participants had been exposed to more than 1 type of Hydrocarbon.
Chlorinated hydrocarbons contain participants exposed to trichloroethylene, carbon tetrachloride, and other chlorinated hydrocarbons (n=10) including perchloroethylene, chloroform and chlorobenzene.
Pure hydrocarbons contain participants exposed to benzene, toulene, xylene, hexane, and petroleum/petroleum derivatives including fuel oil, natural gas, kerosene

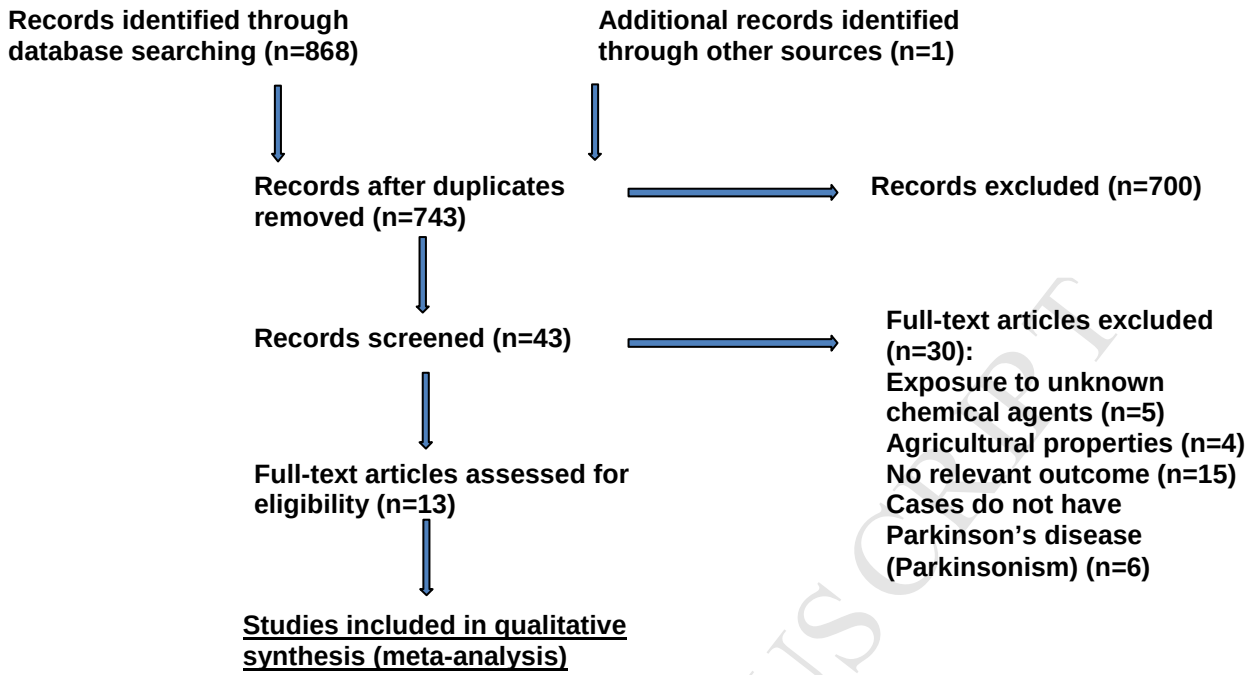

Figure 1- PRISMA flow diagram, process of study selection.

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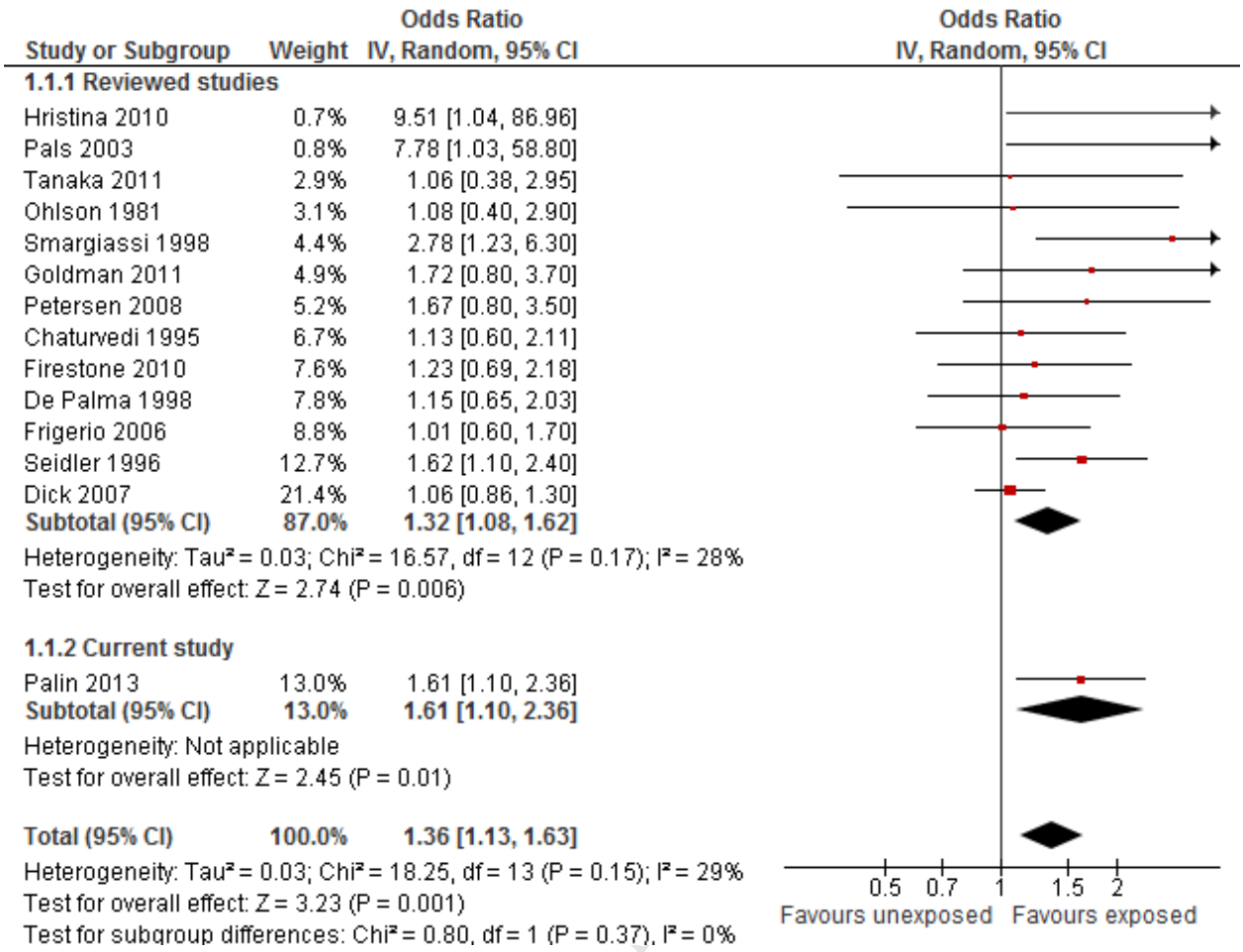

Figure 2 Summary odds ratio from 13 case-control studies, and the PD GEN study of hydrocarbon exposure and Parkinson's disease (ever versus never).

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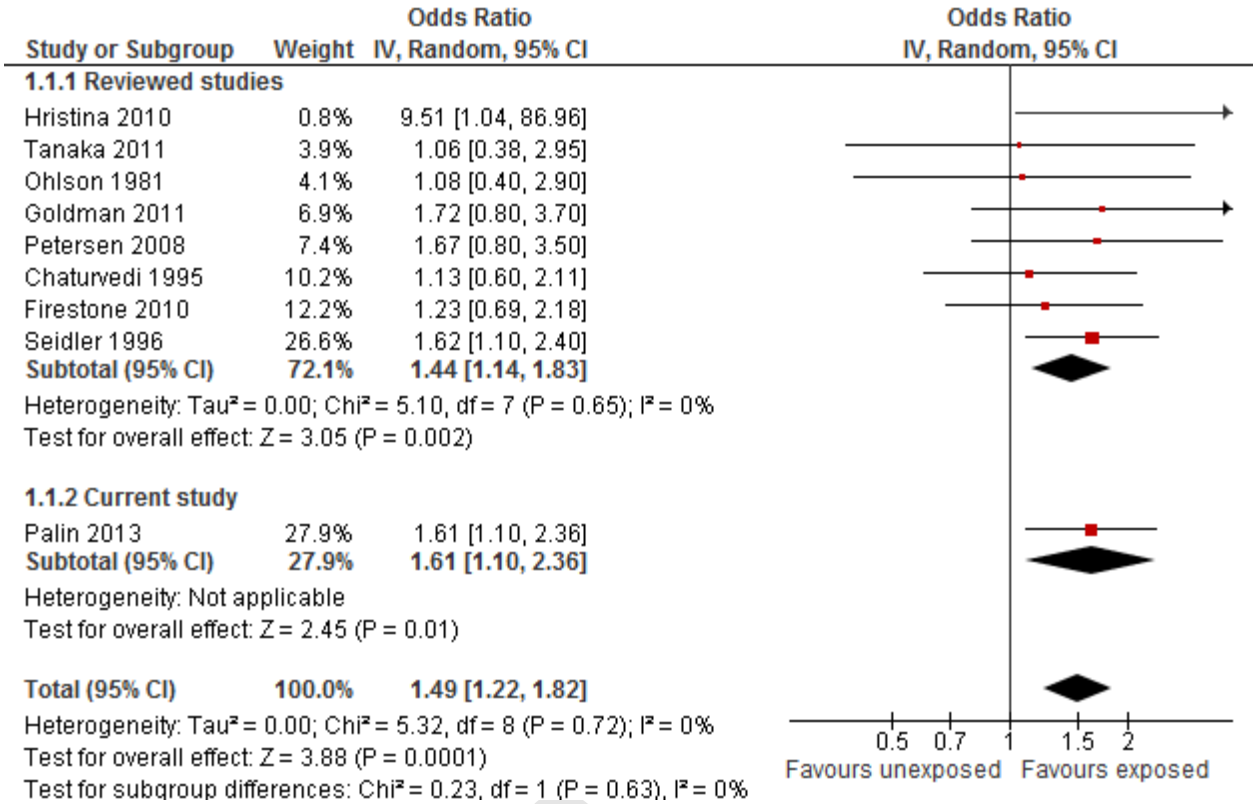

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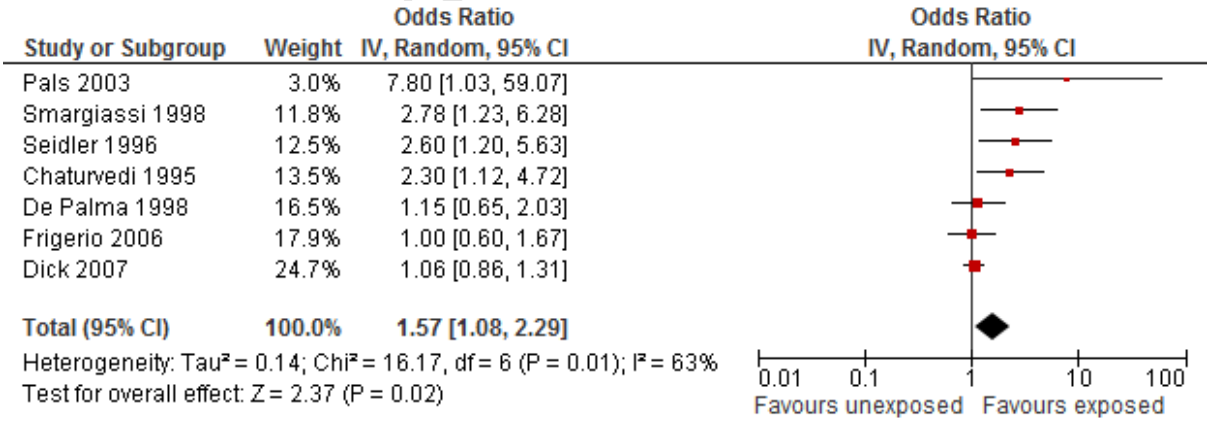

Figure 3 Summary odds ratios from case-control studies of occupational hydrocarbon exposure (A) and non-occupational hydrocarbon exposure (B) and Parkinson's disease (ever versus never).

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We did a systematic review of hydrocarbon exposure and the risk of Parkinson's disease.

We included a new large case-control study of hydrocarbons and Parkinson's disease.

There was a significant association between hydrocarbons and the risk of Parkinson's disease.

Data from prospective studies is required to reinforce this relationship with hydrocarbons.

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Supplementary Table 1 Overview of the studies included in the meta-analyses

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Study	Location	Methods of recording exposure	location of recruitment	Exposure	Exposure ascertainment (Ever/Never)	No. exposed cases/ Total number of cases	No. exposed controls/ Total number of controls	Odds Ratio (95% CI)	Adjustment factors	Other information
Goldman et al (2012)	U.S	Interview	Research Council WWII veteran twins registry	n-hexane, Xylene, Toulene, CCl_4, TCE and PERC	Occupational exposure. 2% of work time or 1 hour per week.	19/99	14/99	1.7 (0.8-3.7) p=0.16	Age, head injury, and zygosity.	Twin study, all male cohort.
Tanaka et al (2011)	Japan	Self-reporting questionnaire	Hospital	Solvents	Occupational exposure. 10hrs per week of more than 1 year.	7/249	12/369	1.10 (0.38-2.95) p=0.91	Age, education, smoking, place of residence.	-
Hristina et al (2010)	Serbia	Interview	University clinical centre	Naphtha and its derivates	Occupational exposure.	13/110	1/220	9.53 (1.04-87.0) p=0.046	Age, sex and smoking	Controls were degenerative joint disease or GIT disease patients.
Firestone et al (2010)	U.S	Interview	Population-based	Solvents	Occupational exposure	156/404	140/526	1.23 (0.69-2.18) p=0.49	Age, sex, smoking, and ethnicity.	OR were presented a separately for gender. We calculated joint OR.
Peterson et al (2008)	Faroe Islands	Interview	Population-based	Solvents	Occupational exposure	19/79	32/154	1.68 (0.80-3.50) p=0.17	Age, sex and smoking	-
Dick et al (2007)	Scotland, Sweden, Italy, Romania and Malta	Interview	Mixture of clinics, hospitals and community.	Solvents	Occupational and hobby exposure. Average Annual Intensity (AAI)	?/767	?/1989	1.06 (0.86-1.30) p=0.60	Age, sex, smoking, PD family history, knocked unconscious, and country.	Five centre case-control study. Larger association with low exposure when compared to high exposure.
Frigerio et al (2006)	U.S	Interview-telephone	Population-based	Paints, varnishes, cleaning products, petroleum derivatives, glues/printing products.	Occupational and hobby exposure	39/149	33/129	1.0 (0.60-1.70) p=0.97	Age and sex	Presented separate OR for gender. Personal communication with authors obtained overall OR.

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Pals et al (2003)	Belgium (Flanders)	Self-reporting questionnaire	PD support groups and spouse controls	Toluene	Over 6 months exposure prior to onset of PD.	23/423	1/205	7.8 (1.03-58.8) p=0.047	Age, sex and PD family history.	-
De Palma et al (1998)	Italy	Self-reporting questionnaire	Hospital	Solvents	Occupational or residential contact for at least 10 consecutive years before PD onset.	24/100	43/200	1.15 (0.65-2.03) p=0.63	-	-
Smargiassi et al (1998)	Italy	Interview	Hospital	Organic solvent	Substantial leisure and jobs. At least 10 consecutive years	23/86	12/86	2.78 (1.23-6.26) p=0.014	-	-
Seidler et al (1996)	Germany	Interview	Clinics, and random neighbourhood and regional controls	Solvents	Occupational exposure. And separate recreational exposure (hobby)	100/376	79/372	1.60 (1.10-2.40) p=0.015	Education and smoking.	Presented a range of products hydrocarbon products. Larger association with hobby exposure.
Chaturvedi et al (1995)	Canada	Self-reporting questionnaire	Population-based	Gasoline, fuels and oils	Occupational exposure And separate recreational exposure (hobby)	23/87	489/2070	1.15 (0.60-2.11) p=0.71	-	Presented a range of products hydrocarbon products. Larger association with hobby exposure.
Ohlson C-G and Hogstedt (1981)	Sweden	Self-reporting questionnaires	2 Hospitals	Solvents	Occupational exposure. 6 months work with solvents	16/91	12/75	1.1 (0.40-2.90) p=0.88	-	Controls were subarachroid hemorrhage patients.

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Supplementary Table 2- *The demographic characteristics of the PD GEN PD cases and carer-controls*

Characteristic	Cases		Control	
	No.	**%**	**No.**	**%**
Participants	1463	68.1	685	31.9
Gender				
Male	973	66.5	174	25.4
Female	490	33.5	511	74.6
Age, mean (SD)	75.2 (9.38)			73.1 (9.71)
Cigarette smoking				
Never smokers	667	47.1	345	52.8
Ever smokers	750	52.9	309	47.2
Pesticide exposure				
Never exposed	1327	91.1	644	94.4
Ever exposed	130	8.9	38	5.6
Caffeine intake, mean (SD)	4.8 (2.0)		5.0 (1.9)	
Place of resident				
Town/city	577	39.5	255	37.5
Countryside	345	23.6	169	24.9
Mixture of both	540	36.9	256	37.6
Ethnicity				
White	1422	97.5	676	98.8
Black	6	0.4	1	0.1
Asian	30	2.1	7	1.0
Parkinson's family history				
No	1302	90.0	640	94.1
Yes	145	10.0	40	5.9

Values calculated by Chi-squared and independent t-test
Missing values:
Smoking- n=77 (3.6%)
Caffeine intake- n=5 (0.2%)
Pesticide exposure- n=9 (0.4%)
Place of Residence- n=6 (0.3%)
Ethnicity- n=5 (0.2%)
PD family history- n=21 (1%)

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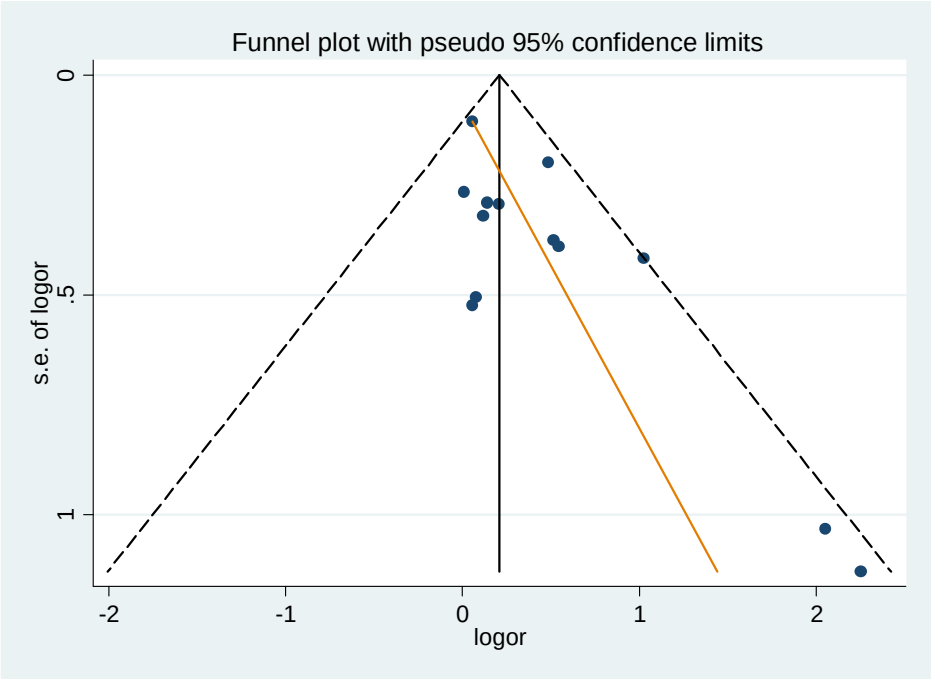
Supplementary Figure 1: Funnel plot with 13 included studies



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