Parkinson's Disease, Multiple Sclerosis, and Commercial Motor Vehicle Driver Safety

Findings of Evidence Report

Developed by

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MANILA Consulting Group, Inc.

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Parkinson's Disease, Multiple Sclerosis and Potential Crash Risk

- Potential risk of a motor vehicle crash among individuals with Parkinson's Disease (PD) or Multiple Sclerosis (MS)
  - Both PD and MS are progressive neurological disorders that may impair driving ability

Key Questions

- **Key Question 1**
  - What are the criteria that define when an individual with Parkinson's disease (PD) should stop driving a CMV?
- **Key Question 2**
  - What is the impact of pharmacotherapy for PD on driver safety?

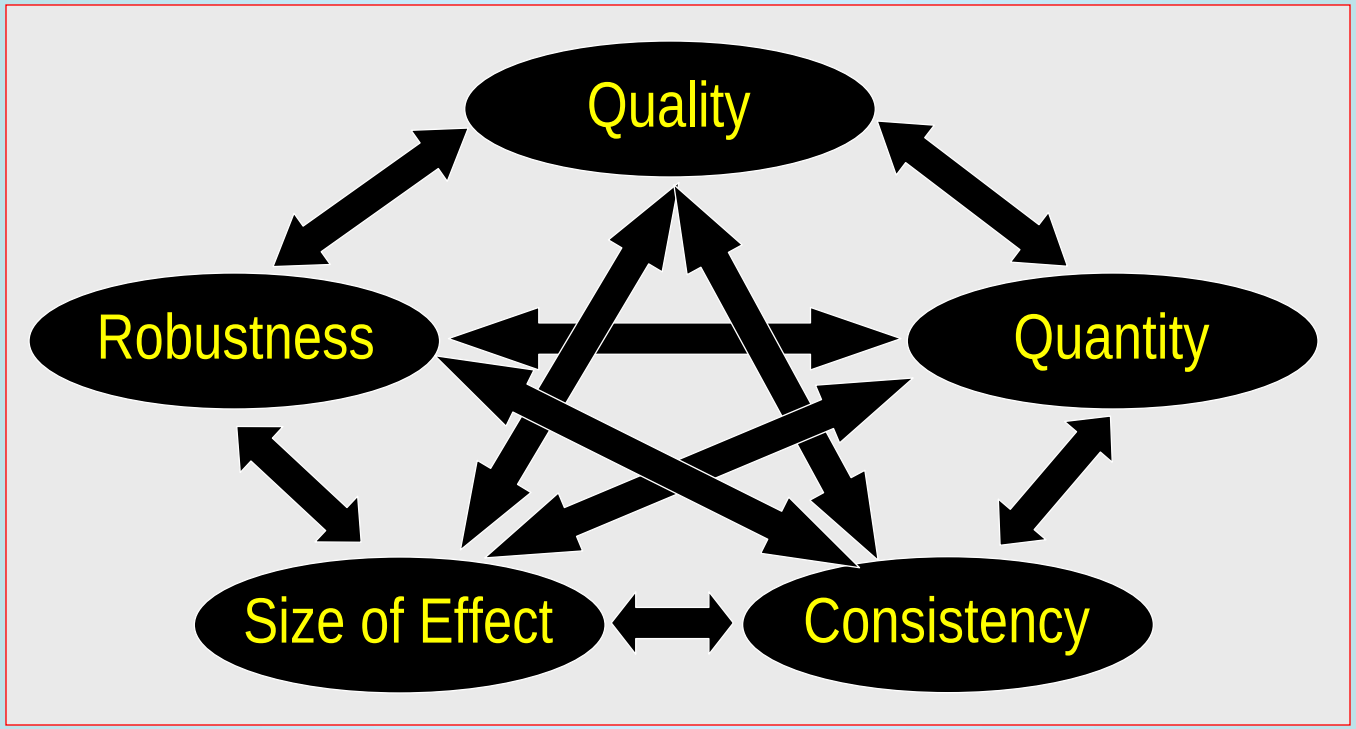
Key Questions

- **Key Question 3**
  - Are individuals with Multiple Sclerosis (MS) at an increased risk for a motor vehicle crash?
- **Key Question 4**
  - What factors associated with MS are predictive of an increased crash risk?

Key Questions

- **Key Question 5**
  - How frequently should an individual with MS be assessed in order to monitor whether they remain safe to drive?
- **Key Question 6**
  - What is the impact of pharmacotherapy for MS on driver safety?

Strength of Evidence Ratings



Strength of Evidence Ratings

Strength of Evidence	Interpretation
Qualitative Conclusion	
Strong	Evidence supporting the qualitative conclusion is convincing. It is highly unlikely that new evidence will lead to a change in this conclusion.
Moderate	Evidence supporting the qualitative conclusion is somewhat convincing. There is a small chance that new evidence will overturn or strengthen our conclusion. ECRI recommends regular monitoring of the relevant literature for moderate-strength conclusions.
Minimally Acceptable	Although some evidence exists to support the qualitative conclusion, this evidence is tentative and perishable. There is a reasonable chance that new evidence will either overturn or strengthen our conclusions. ECRI recommends frequent monitoring of the relevant literature.
Insufficient	Although some evidence exists, the evidence is insufficient to warrant drawing an evidence-based conclusion. ECRI recommends frequent monitoring of the relevant literature.
Quantitative Conclusion	
High	The estimate of treatment effect in the conclusion is stable. It is highly unlikely that the magnitude of this estimate will change substantially as a result of the publication of new evidence.
Moderate	The estimate of treatment effect the conclusion is somewhat stable. There is a small chance that the magnitude of this estimate will change substantially as a result of the publication of new evidence. ECRI recommends regular monitoring of the relevant literature.
Low	The estimate of treatment effect included in the conclusion is likely to be unstable. There is a reasonable chance that the magnitude of this estimate will change substantially as a result of the publication of new evidence. ECRI recommends frequent monitoring of the relevant literature.
Unstable	Estimates of the treatment effect are too unstable to allow a quantitative conclusion to be drawn at this time. ECRI recommends frequent monitoring of the relevant literature.

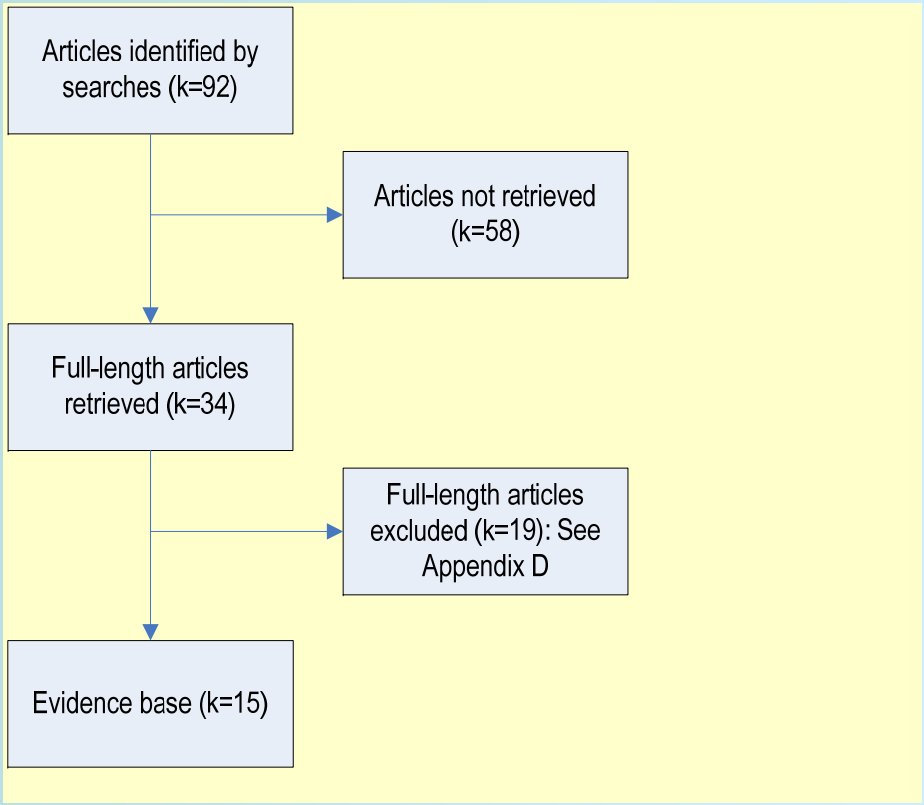
Quality of Individual Studies and Body of Evidence

- For most studies, individual study quality was graded using revised Newcastle-Ottawa scales for case-control studies and cohort studies
- Overall quality grade for each evidence base was determined using the median quality score of the individual studies

Searches

Name of database	Date limits	Platform/provider
CINAHL (Cumulative Index to Nursing and Allied Health Literature)	Through April 23 2008	OVID
Cochrane Library	Through 2008 Issue 2	www.thecochranelibrary.com
Embase (Excerpta Medica)	Through April 23 2008	OVID
Medline	Through April 23 2008	OVID
PubMed (Pre Medline)	Searched April 23 2008	www.pubmed.gov
TRIS Online (Transportation Research Information Service Database)	Searched December 11 2007	http://trisonline.bts.gov/search.cfm
PsycINFO	Through April 23 2008	OVID
National Guideline Clearinghouse™ (NGC™)	Searched December 17 2007	www.ngc.gov
Health Technology Assessment Database (HTA)	Through 2008 Issue 2	www.thecochranelibrary.com

Key Question 1:
Parkinson's Disease and Driver Safety



- 15 studies included
- No CMV drivers
- 13 Cohort , 1 Survey, 1 Case control
- 3 crash, 11 driving performance, 1 daytime sleepiness

Key Question 1: Study Populations

Reference	Study design	How was PD defined?	PD clinically confirmed?	Factors controlled for?	Outcome(s) self-reported?
Crash studies					
Dubinsky et al. 1991	Case-control	H&Y stage	Yes	No	Yes
Meindorfner 2005	Survey	Combined H&Y stage	No. Self report	No	Yes
Adler et al. 2000	Cohort	NR	NR	Yes (age, gender, education, residence)	Yes
Excessive daytime sleepiness studies					
Hobson et al. 2002	Cohort	High function PD; H&Y stage; clinical diagnosis with no cognitive impairment; medication working	Yes	No	Yes
Driving performance studies					
Devos et al. 2007	Cohort	H&Y stage	Yes	Yes (age and gender)	No
Singh et al. 2007	Cohort	H&Y stage	Yes	No	No
Uc et al. 2007, 2006	Cohort	H&Y score	Yes	NR	No
Stolwyk et al. 2006, 2005	Cohort	Medical assessment with no other neurological impairments	Yes	NR	No
Worringham et al.2005 Wood et al. 2005	Cohort	H&Y stage, UPDRS rating	Yes	Yes (age)	No
Zesiewicz et. al. 2002	Cohort	H&Y stage, UPDRS rating	Yes	No	No
Heikkila et al. 1998	Cohort	H&Y stage	Yes	Yes (age)	No

Key Question 1: Study Generalizability

- Generalizability of these studies to CMV drivers may be limited.
- CMV drivers have greater risk exposure than non-CMV drivers.
- Women are overrepresented relative to the CMV driver population.
- Average age of enrollees somewhat older (62 to 73) than the average age of the CMV driver population

Key Question 1: Parkinson's Disease and Driver Safety

- Direct Evidence (Crash Studies)
  - Each of these studies addressed factors associated with PD that may increase crash risk.
  - All were rated as low quality.

Key Question 1: Parkinson's Disease and Driver Safety - Results

Reference	Explanatory Variables	Odds ratio (95% CI)	p-value
Meindorfner 2005	Moderate (vs. minor) disease severity	1.42 (1.12-1.81)	<0.005
	Advanced (vs. minor) disease severity	1.51 (1.05-2.18)	<0.050
	Sudden onset of sleep (SOS) at the wheel	3.16 (2.33-4.30)	<0.001
	Km per year ≥ (vs. <) 6,000	1.49 (1.18-1.88)	<0.005

Multiple regression analysis not performed, so findings not definitive

Key Question 1: Parkinson's Disease and Driver Safety - Results

Reference	Crash rate – PD drivers	Crash rate – normal controls	Rate ratio (95% CI)	p-value
Dubinsky et al. 1991	H&Y Stage 1			
	0.056	0.115	0.487 (0.119-1.985)	0.315
	H&Y Stage 2			
	0.384	0.115	3.339 (1.600-6.967)	0.001
	H&Y Stage 3			
	0.373	0.115	3.240 (1.360-7.717)	0.008

Multiple regression analysis not performed, so findings not definitive

Key Question 1: Parkinson's Disease and Driver Safety - Results

Reference	Explanatory Variables	Odds ratio (95% CI)	p-value
Adler et al. 2000	Movement restriction	3.2 (1.1-9.4)	0.034

Logistic regression analysis found that PD drivers with movement restriction more likely to crash than those without movement restriction. However, this is a single small study that bears replication.

Key Question 1: Parkinson's Disease and Driver Safety - Results

- Indirect evidence (daytime sleepiness study)
  - Hobson et al. performed a multivariable regression analysis and found that scores on two sleep questionnaires were significantly associated with falling asleep while driving among individuals with PD ($p < 0.001$).
  - Other variables (Hoehn and Yahr score, Mini-Mental State Examination score, leg movements in sleep, anti-Parkinson medication, and use of a sleeping aid) did not show significant association in the multivariable analysis.

Key Question 1: Parkinson's Disease and Driver Safety - Results

- Indirect evidence (driving performance studies)
  - 11 cohort studies
  - 9 moderate quality, 2 low quality
  - 3 measured factors associated with road test outcomes (pass/fail or suitable/not suitable)
  - 5 measured factors associated with specific on-road driving performance tasks
  - 3 measured factors associated with simulated driving performance

Key Question 1: Parkinson's Disease and Driver Safety - Results

- Indirect evidence (driving performance studies)
  - 11 cohort studies
  - 8 studies performed multivariable analyses
  - Studies identified stage of PD, duration of PD, decreased motor and cognitive function as potential risk factors
  - However, prediction of road test outcome is not the same as prediction of crash

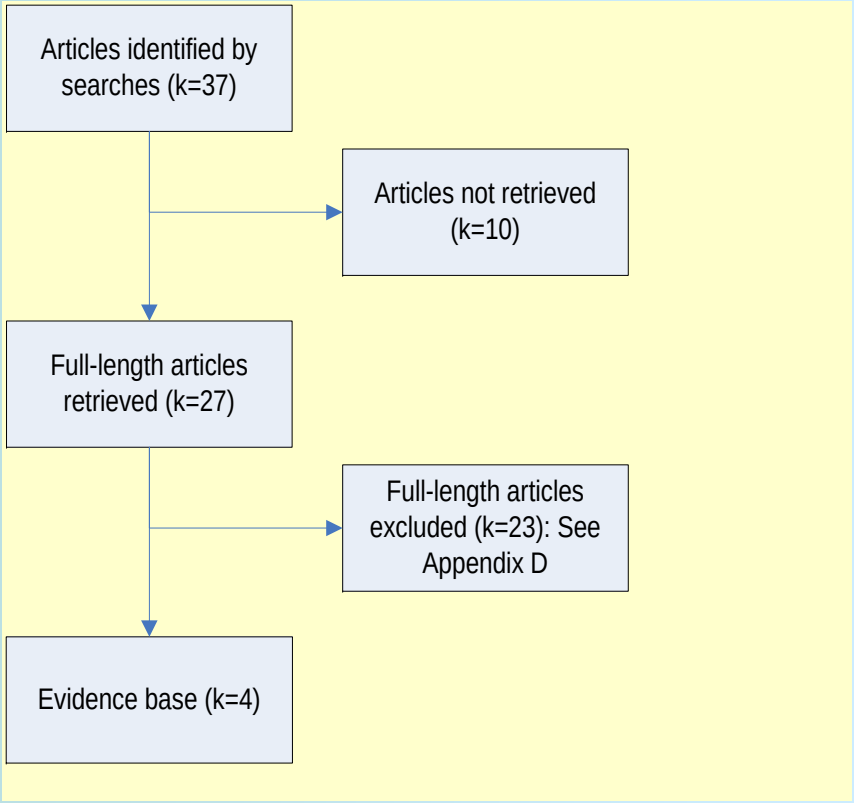
Key Question 1: Parkinson's Disease and Driver Safety - Summary

- **The evidence is insufficient to determine with precision what risk factors or combination of risk factors truly defines when an individual with PD should stop driving. However, potential risk factors include movement restriction/decreased motor function, stage of PD, duration of PD, decreased cognitive function, and sudden onset of sleepiness (Strength of Evidence: Minimally Acceptable).**

Key Question 2: Impact of PD Pharmacotherapy on Driver Safety

- Pharmacotherapy may affect cognitive and psychomotor abilities that could contribute to crash risk
  - Dopamine agonists
  - Dopamine prodrugs
  - COMT inhibitors
  - MAO-B inhibitors
  - Amantadine
  - Anticholinergics

Key Question 2: Impact of PD Pharmacotherapy on Driver Safety



- 4 studies included
- No CMV drivers
- 3 RCTs, 1 cohort
- Quality = 1 high, 3 moderate

Key Question 2: Study Characteristics

Reference	Study design	Pharmacotherapy evaluated in study	How was PD defined?	PD clinically confirmed?	Outcome(s) self-reported?
Sethi et al. 1998	Double-blind cohort extension study	Dopamine Agonist (Ropinirole) vs. Placebo	H&Y Stage	Yes	Yes
Adler et al. 1997	Double-blind RCT	Dopamine Agonist (Ropinirole) vs. Placebo	H&Y Stage	Yes	Yes
Parkinson Study Group 1997	Double-blind RCT	Dopamine Agonist (Pramipexole) vs. Placebo	Early Idiopathic PD <7 years in H&Y Stages I-II	Yes	Yes
Shannon et al. 1997	Double-blind RCT	Dopamine Agonist (Pramipexole) vs. Placebo	Idiopathic PD individuals in H&Y Stages I-III	Yes	Yes

Key Question 2: Study Generalizability

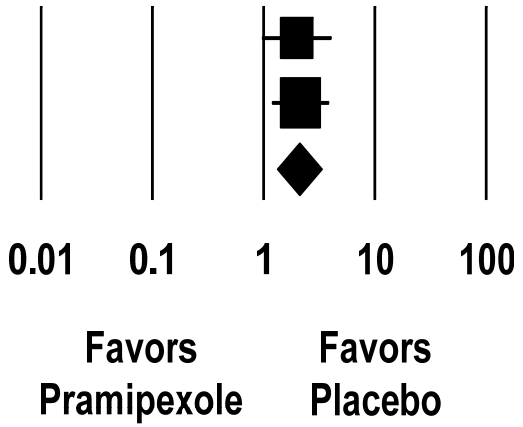
- Generalizability to CMV drivers may be limited.
- CMV drivers have greater risk exposure than non-CMV drivers.
- Women are overrepresented relative to CMV population
- CMV drivers are under more pressure to drive even if they are experiencing side effects of medications.
- Dopamine agonists were the only drug class evaluated in these studies

KQ2: Impact of PD Pharmacotherapy on Driver Safety - Results

- No studies directly evaluated crash risk (no crash data)
- All studies evaluated effects of dopamine agonists on sleepiness in patients with PD
- One RCT (plus an extension study) found significant elevated risk of somnolence associated with ropinirole
- We combined data from 2 RCTs (both evaluating pramipexole) in a meta-analysis

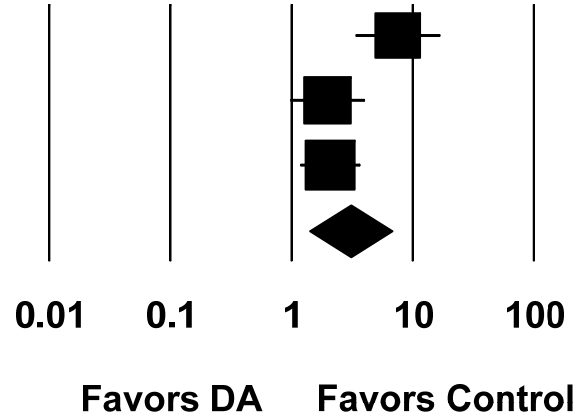
KQ2: Impact of Pramipexole on Driver Safety - Results

Study name	Risk ratio	Lower limit	Upper limit	p-Value
Parkinson Study Group	1.984	0.963	4.085	0.063
Shannon et al.	2.086	1.166	3.731	0.013
Summary Effect	NC	1.300	3.217	0.002



KQ2: Impact of Dopamine Agonists on Driver Safety - Results

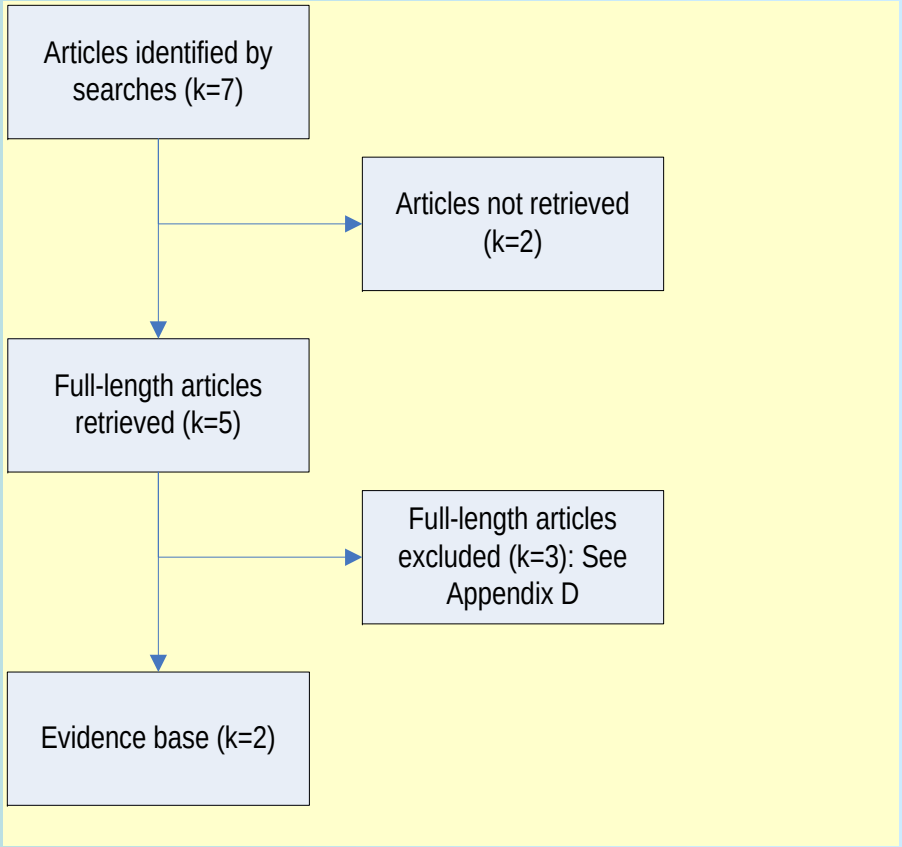
Study name	Risk ratio	Lower limit	Upper limit	p-Value
Adler	7.543	3.331	17.079	0.000
Parkinson Study	1.984	0.963	4.085	0.063
Shannon	2.086	1.166	3.731	0.013
Summary Effect	NC	1.385	6.667	0.006



KQ2: Impact of PD Pharmacotherapy on Driver Safety - Summary

- **Evidence suggests that use of dopamine agonists may lead to somnolence (sleepiness) in individuals with PD. (Strength of Evidence: Moderate) The evidence is insufficient to determine whether other types of pharmacotherapy may affect driver safety. Whether measures of somnolence among individuals with PD taking pharmacotherapy can predict actual crash risk cannot be determined from currently available evidence.**

Key Question 3:
Multiple Sclerosis and Crash Risk



- 2 studies included
- Both cohort studies
- Quality = moderate

Key Question 3: Study Characteristics

Reference	Study design	How was MS defined?	Severity of MS	Factors adjusted for	Outcome(s) self-reported?
Lings 2002	Cohort	Diagnosis of MS 340 (ICD 8th revision)	Not reported	Age, gender, residence, exposure period (driver license period)	No
Schultheis et al. 2002	Cohort	Relapsing-remitting (59%), secondary progressive (7%), primary progressive (4%), or undefined course (30%)	Minimal or no physical limitation	Age, gender, and years of driving	No

Key Question 3:Study Generalizability

- Generalizability of these studies to CMV drivers may be limited.
- CMV drivers have greater risk exposure than non-CMV drivers.
- Women are highly overrepresented relative to the CMV driver population.
- Average age of enrollees is within the age range of the CMV driver population

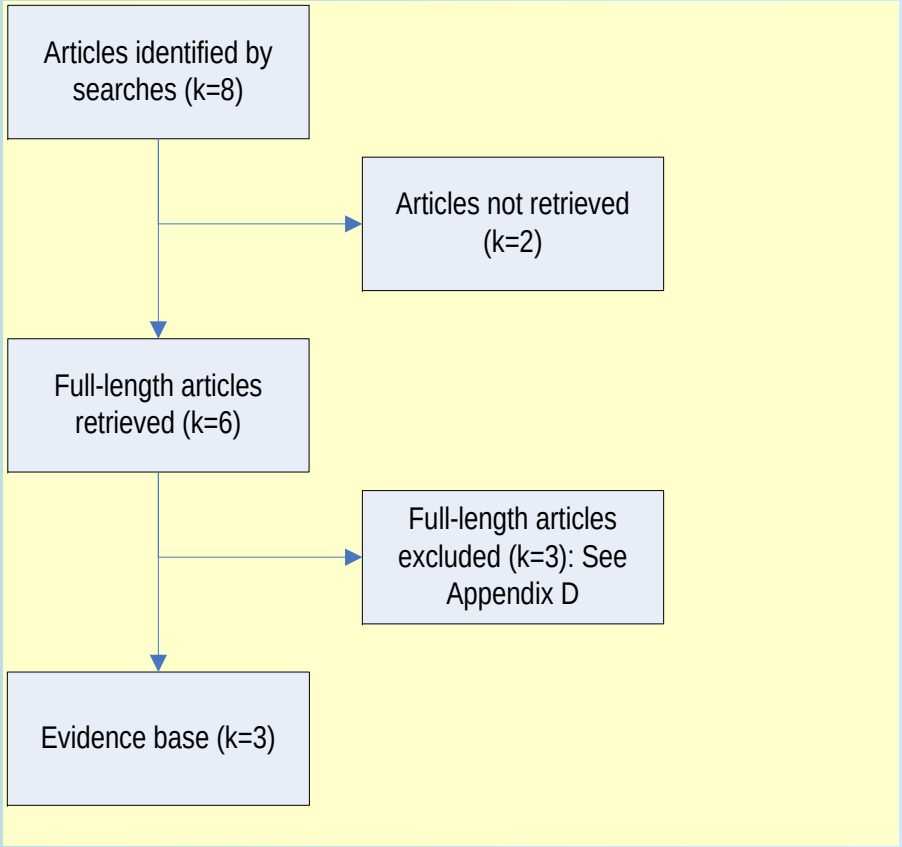
Key Question 3: Multiple Sclerosis and Crash Risk - Results

- Although both studies showed an elevated risk of crash, the difference did not reach statistical significance in either study
  - Schultheis et al. – OR 6.74 (95% CI 0.76-59.74), p = 0.087
  - Lings – rate ratio 3.4 (95% CI 0.73-17.15), p = 0.129
  - However, a subgroup analysis by Schultheis suggests that individuals with MS plus additional impairment may have an increased risk of crash

KQ3: Multiple Sclerosis and Crash Risk - Summary

- **Currently available evidence is insufficient to determine whether crash risk is increased among individuals with MS. However, the possibility that crash risk is increased among a subgroup of individuals with MS and an additional impairment cannot be ruled out.**

Key Question 4:
Factors Predictive of Crash Risk (MS)



- 3 studies included
- All cohort studies
- Quality = moderate

Key Question 4: Study Characteristics

Reference	Study design	How was MS defined?	Severity of MS	Factors adjusted for	Outcome(s)
Schultheis et al. 2002	Cohort	Relapsing-remitting (59%), secondary progressive (7%), primary progressive (4%), or undefined course (30%)	Minimal or no physical limitation	Age, gender, and years of driving	Crash
Lincoln and Radford 2008	Cohort	Clinic assessment	Difficulty walking (38%), assistance with mobility required (24%), wheelchair bound (15%), independently mobile (24%)	NR	Road test performance
Schultheis et al. 2001	Cohort	Relapsing-remitting (61%), secondary progressive (7%), primary progressive (4%), or undefined course (29%)	Minimal or no physical limitation	Age, gender, and years of driving	Simulated driving performance

Key Question 4:Study Generalizability

- Generalizability of these studies to CMV drivers may be limited.
- CMV drivers have greater risk exposure than non-CMV drivers.
- Women are highly overrepresented relative to the CMV driver population.
- Average age of enrollees is within the age range of the CMV driver population

Key Question 4: Factors Predictive of Crash Risk (MS) - Results

- Direct evidence (crash study)
  - Schultheis et al. (2002) found significantly increased crash risk among drivers with MS and cognitive impairment (MS+) but not among drivers with MS but no cognitive impairment (MS-)
  - MS+ OR 18.67 (95% CI 1.88-185.4), p = 0.012
  - MS- OR 1.23 (95% CI 0.07-21.64), p = 0.887

Key Question 4: Factors Predictive of Crash Risk (MS) - Results

- Indirect evidence (road test performance study)
  - Lincoln and Radford found that MS patients who failed a road test scored significantly worse ($p < 0.05$) on 6 out of 23 cognitive tests than patients who passed a road test

Key Question 4: Factors Predictive of Crash Risk (MS) - Results

- Indirect evidence (simulated driving performance study)
  - Schultheis et al. (2001) tested individuals with MS on Useful Field of Vision (UFOV) driving test and the Neurocognitive Performance Test (NDT)
  - Individuals with MS plus cognitive impairment had a significantly higher estimated crash risk on the UFOV test compared to healthy controls. MS patients without cognitive impairment did not differ significantly from healthy controls.

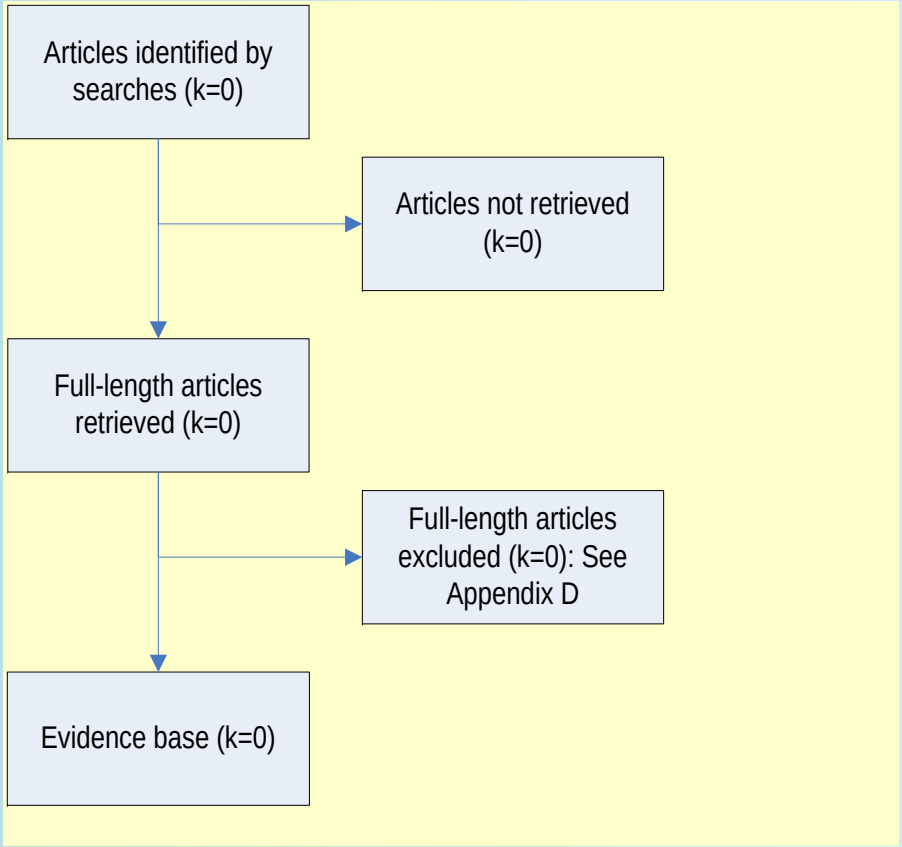
Key Question 4: Factors Predictive of Crash Risk (MS) - Results

- Indirect evidence (simulated driving performance study)
  - Individuals with MS plus cognitive impairment had significantly longer latency times on NDT than MS without cognitive impairment or healthy controls.
  - No significant difference in error rates on NDT among the three comparison groups.

KQ4: Factors Predictive of Crash Risk (MS) - Summary

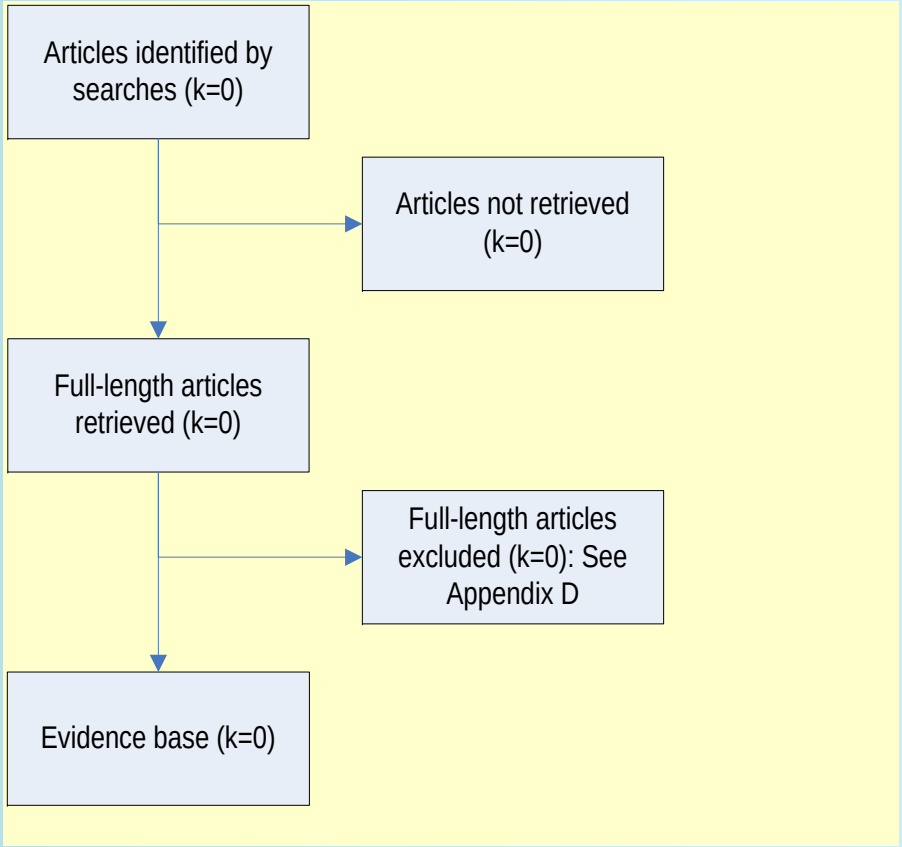
- **The available evidence is insufficient to determine whether factors associated with MS are predictive of increased crash risk among individuals with MS. However, the possibility that crash risk is increased among a subgroup of individuals with MS and cognitive impairment cannot be ruled out.**

Key Question 5: Frequency of Driver Safety Assessment for MS Patients



- **No evidence was identified that addressed this question. Therefore, no evidence-based conclusion is possible at the present time.**

Key Question 6: Impact of MS Pharmacotherapy on Driver Safety



- **No evidence was identified that addressed this question. Therefore, no evidence-based conclusion is possible at the present time.**