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Special Report 23

Systematic Review and Meta-analysis of Selected Health Effects of Long-Term Exposure to Traffic-Related Air Pollution

HEI Panel on the Health Effects of Long-Term Exposure to Traffic-Related Air Pollution

Chapter 13: Traffic-Related Air Pollution and Neurodegenerative Outcomes

These Appendices were reviewed solely for spelling, grammar, and cross-references to the main text. They have not been formatted or fully edited by HEI. This document was part of the HEI Panel's review process.

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Appendices Chapter 13: Additional Tables and Discussion
Traffic-Related Air Pollution and Neurodegenerative Outcomes

Appendix 13A Cognitive function and cognitive decline

Table 13A-1. Key study characteristics of studies included in the narrative review for cognitive function and cognitive decline in adults – pollutants and indirect traffic measures (*N*=8).

Reference	Study Name	Location	Study Design	Study period	Sample Size	Mean age baseline (years)	Sex	Exposure Assessment	Exposure window and timing tests	Pollutant(s)	Outcome
Colicino 2014	VA Normative Aging Study	Boston, Massachusetts, United States	Cohort	1995–2007	582 and 387	72	Male	LUR	One year average prior to test. Tests administered at 3–5 years intervals. Average 1.8 tests	EC	Cognitive decline
Oudin 2017	Betula	Umea, Sweden	Cohort	1988–2010	1,469	69	Both	LUR	Cumulative average over study period. Test administered at 5-year intervals; average 2.5 tests	NO_x	Cognitive decline
Power 2011	VA Normative Aging Study	Boston, Massachusetts, United States	Cohort	1996–2007	671	71	Male	LUR	One year average prior to test. Tests administered at 3 years intervals; average 2.14 tests	EC	Cognitive function
Ranft 2009	SALIA	Ruhr Areas, Germany	Cross sectional	2007–2008	396	54–55	Female	Distance or density	Exposure at baseline residential address level (1980) using 2000 traffic data and limited to people that did not move addresses. Single test was administered in 2007–2008	Distance	Cognitive function
Schikowski 2015	SALIA	Ruhr Areas, Germany	Cross sectional	2007–2009	789	55	Female	Distance or density, LUR	Annual average using ESCAPE 2008–2009. Single test was administered in 2007–2009	Density, NO_2, NO_x, EC, PM_{10} mass, $PM_{2.5}$ mass	Cognitive function
Tonne 2014	Whitehall II	London, United Kingdom	Cross sectional, Cohort	2002–2009	2,791	61	Both	Dispersion / CTM	5-year average prior to second test. Test was administered twice with a 5-year interval	PM_{10} traffic, $PM_{2.5}$ traffic	Cognitive function, Cognitive decline
Tzivian 2016a	HNR	Ruhr Areas, Germany	Cross sectional	2006–2008	3,085	64	Both	Distance or density, LUR	Annual average using ESCAPE 2008–2009. Single test was administered in 2006–2008	Density, NO_2, NO_x, EC, PM_{10} mass, PM_{coarse} mass, $PM_{2.5}$ mass	Cognitive function
Wellenius 2012	MOBILIZE	Boston, Massachusetts, United States	Cohort	2005–2008	765	78.1	Both	Distance or density, LUR	One year average prior to test. Test was administered twice with a 1.5-year interval	Distance, EC	Cognitive function

Table 13A-2. Associations of $PM_{2.5}$ mass with cognitive function and cognitive decline.

Reference	Study Name	Location	Study Design	Study period	Sample size	Mean age baseline (years)	Sex	Mean or median exposure [a,b]	Outcome	Neuropsychological tests (direction[c])	Effect measure	Effect Estimate (95% CI)	Increment
Schikowski 2015	SALIA	Ruhr Areas, Germany	Cross sectional	2007–2009	789	55	Female	17.4	Cognitive function	Global cognition; CERAD-Plus (-)	mean difference	0.31 (−1.11 to 1.72)	1.9 µg/m³
										Semantic memory: semantic fluency (-)		0.07 (−0.06 to 0.20)	
										Global cognition: MMSE (-)		0.07 (−0.10 to 0.25)	
										Semantic memory: Boston naming test (-)		−0.09 (−0.26 to 0.07)	
										Semantic memory: phonetic fluency (-)		0.06 (−0.10 to 0.22)	
										Episodic memory: word list learning (-)		0.11 (−0.06 to 0.27)	
										Episodic memory: word list recall (-)		0.10 (−0.07 to 0.26)	
										Constructional praxis: figure copying (-)		−0.19 (−0.38 to 0.01)	
										Constructional praxis: figure recall (-)		0.06 (−0.10 to 0.22)	
										Executive function: trail-making A (-)		−0.05 (−0.19 to 0.09)	
										Executive function: trail-making B (-)		−0.02 (−0.16 to 0.12)	
										Executive function: trail-making B/A (-)		0.03 (−0.11 to 0.17)	
Tzivian 2016a	HNR	Ruhr Areas, Germany	Cross sectional	2000–2008	3,085	64	Both	18.4	Cognitive function	Global cognitive score (-)	mean difference	−0.28 (−0.42 to −0.15)	1.44 µg/m³
										Verbal fluency (-)		−0.07 (−0.11 to −0.03)	
										Labyrinth test (problem-solving/processing speed) (-)		−0.09 (−0.13 to −0.04)	
										Immediate recall (verbal memory) (-)		−0.05 (−0.09 to −0.01)	
										Delayed recall (verbal memory) (-)		−0.06 (−0.10 to −0.01)	
										Clock drawing test (dichotomous, abstraction/visual-spatial organization	odds ratio (OR)	0.95 (0.86 to 1.06)	

[a] Unit in the increment column.

[b] Exposure assessment was LUR.

[c] A negative direction (-) means that a lower score indicates poorer cognitive function; a positive direction (+) means that a higher score indicates poorer cognitive function. Ratio measures (RRs, ORs, IRRs) >1.0 indicate higher risk for the outcome.

Table 13A-3. Associations of EC with cognitive function and cognitive decline.

Reference	Study Name	Location	Study Design	Study period	Sample size	Mean age baseline (years)	Sex	Pollutant	Mean or median exposure[a, b]	Outcome	Neuropsychological tests (direction[c])	Effect measure	Effect Estimate (95% CI)	Increment
Colicino 2014	VA Normative Aging Study	Boston, Massachusetts, United States	Cohort	1995–2007	387	72	Male	BC	0.6	Cognitive decline	Change in MMSE score from first cognitive assessment (-)	mean difference	0.13 (−0.11 to 0.37)	doubling
Power 2011	VA Normative Aging Study	Boston, Massachusetts, United States	Cohort	1996–2007	671	71	Male	BC	0.58	Cognitive function	Low cognitive function, MMSE score ≤25	odds ratio (OR)	1.3 (1.1 to 1.6)	doubling
											General cognitive function: global analysis estimate: CERAD), (WAIS-R), the Neurobehavioral Evaluation System2, Developmental Test of Visual-Motor Integration (-)	mean difference	–0.05 (–0.10 to –0.01)	
Schikowski 2015	SALIA	Ruhr Areas, Germany	Cross sectional	2007–2009	789	55	Female	$PM_{2.5abs}$	1.3	Cognitive function	Global cognition; CERAD (-)	mean difference	0.21 (−0.65 to 1.08)	0.4 1×10^{-5}/m
											Global cognition: MMSE (-)		0.02 (−0.08 to 0.13)	
											Semantic memory: semantic fluency (-)		0.01 (−0.07 to 0.09)	
											Semantic memory: Boston naming test (-)		0.01 (−0.09 to 0.11)	
											Semantic memory: phonetic fluency (-)		0.02 (−0.08 to 0.12)	
											Episodic memory: word list learning (-)		0.05 (−0.05 to 0.15)	
											Episodic memory: word list recall (-)		0.04 (−0.06 to 0.14)	
											Constructional praxis: figure copying (-)		−0.12 (−0.24 to 0.01)	
											Constructional praxis: figure recall (-)		0.02 (−0.07 to 0.12)	
											Executive function: trail-making A (-)		−0.02 (−0.10 to 0.07)	
											Executive function: trail-making B (-)		0.03 (−0.06 to 0.12)	
											Executive function: trail-making B/A (-)		0.05 (−0.04 to 0.14)	

Tzivian 2016a	HNR	Ruhr Areas, Germany	Cross sectional	2006–2008	3,085	64	Both	$PM_{2.5abs}$	1.58	Cognitive function	Global cognitive score (-)	mean difference	−0.12 (−0.22 to −0.02)	0.35 1×10^{-5}/m
											Verbal fluency (-)		−0.04 (−0.07 to −0.01)	
											Labyrinth test (problem-solving/processing speed) (-)		−0.03 (−0.06 to −0.01)	
											Immediate recall (verbal memory) (-)		−0.03 (−0.06 to 0.01)	
											Delayed recall (verbal memory) (-)		−0.09 (−0.06 to 0.01)	
											Clock drawing test (dichotomous, abstraction/visual-spatial organization).	odds ratio (OR)	0.99 (0.91 to 1.07)	
Wellenius 2012	MOBILIZE	Boston, Massachusetts, United States	Cohort	2005–2008	765	78	Both	BC	0.36	Cognitive function	Low MMSE score (<25)	odds ratio (OR)	1.15 (0.99 to 1.34)	0.11 µg/m^3
											Immediate recall: Hopkins Verbal Learning Test-Revised (HVLT-R) (-)	mean difference	−0.36 (−0.71 to −0.01)	
											Delayed recall: (HVLT-R) (-)		−0.14 (−0.37 to 0.09)	
											Recognition: (HVLT-R) (-)		0.03 (−0.12 to 0.17)	
											Letter Fluency (-)		−0.26 (−1.04 to 0.53)	
											Category Fluency (-)		0.05 (−0.26 to 0.35)	
											Clock-in-the-Box (-)		−0.04 (−0.13 to 0.05)	
											Trailmaking Test Part A (-)		0.59 (−2.17 to 3.35)	
											Trailmaking Test Part B (-)		2.51 (−2.91 to 7.94)	
											Trailmaking Test Delta(B-A) (-)		2.23 (−2.11 to 6.57)	

[a] Unit in the increment column.

[b] Exposure assessment was LUR.

[c] A negative direction (-) means that a lower score indicates poorer cognitive function; a positive direction (+) means that a higher score indicates poorer cognitive function. Ratio measures (RRs, ORs, IRRs) >1.0 indicate higher risk for the outcome**.**

Table 13A-4. Associations of PM_{10}, PM_{coarse}, and PM components with cognitive function and cognitive decline.

Reference	Study Name	Location	Study Design	Study period	Sample size	Mean age baseline (years)	Sex	Exposure assessment	Pollutant	Mean or median exposure[a]	Outcome	Neuropsychological tests (direction[b])	Effect measure	Effect Estimate (95% CI)	Increment
Schikowski 2015	SALIA	Ruhr Areas, Germany	Cross sectional	2007–2009	789	55	Female	LUR	PM_{10} mass	26.4	Cognitive function	Global cognition; CERAD-Plus (-) Global cognition: MMSE (-) Semantic memory: semantic fluency (-) Semantic memory: Boston naming test (-) Semantic memory: phonetic fluency (-) Episodic memory: word list learning (-) Episodic memory: word list recall (-) Constructional praxis: figure copying (-) Constructional praxis: figure recall (-) Executive function: trail-making A (-) Executive function: trail-making B (-) Executive function: trail-making B/A (-)	mean difference	0.32 (−0.68 to 1.33) 0.07 (−0.06 to 0.20) 0.02 (−0.07 to 0.12) −0.05 (−0.17 to 0.07) 0.01 (−0.10 to 0.13) 0.11 (−0.01 to 0.23) 0.06 (−0.05 to 0.18) −0.15 (−0.29 to −0.01) 0.02 (−0.10 to 0.13) 0.00 (−0.10 to 0.10) 0.01 (−0.09 to 0.11) 0.01 (−0.09 to 0.11)	2.2 µg/m³
Tonne 2014	Whitehall II	London, United Kingdom	Cross sectional	2002–2009	2,791	61	Both	Dispersion / CTM	PM_{10} traffic	0.72	Cognitive function (second test)	Reasoning score on Alice Helm 4-1 test (-) Memory score on 20-word free-recall test (-) Semantic fluency (animal words recall) (-) Phonemic fluency (recall words (-)	mean difference	−0.03 (−0.06 to 0.00) −0.02 (−0.06 to 0.02) 0.01 (−0.03 to 0.05) 0.01 (−0.03 to 0.05)	0.30 µg/m³
									$PM_{2.5}$ traffic	0.64		Reasoning score on Alice Helm 4-1 test (-) Memory score on 20-word free-recall test (-) Semantic fluency (animal words recall) (-) Phonemic fluency (recall words (-)		−0.03 (−0.06 to 0.00) −0.02 (−0.06 to 0.02) 0.01 (−0.03 to 0.05) 0.01 (−0.03 to 0.05)	0.27 µg/m³
			Cohort						PM_{10} traffic	0.72	Cognitive decline	5-year change in reasoning score on Alice Helm 4-1 test (-)		−0.01 (−0.03 to 0.01)	0.30 µg/m³

												5-year change in memory score on 20-word free-recall test (-)		–0.01 (–0.05 to 0.03)	
												5-year change in semantic fluency (-)		0.01 (–0.03 to 0.04)	
												5-year change in phonemic fluency (-)		0.00 (–0.01 to 0.03)	
									$PM_{2.5}$ traffic	0.64		5-year change in reasoning score on Alice Helm 4-1 test (-)		–0.01 (–0.03 to 0.01)	0.27 µg/m³
												5-year change in memory score on 20-word free-recall test (-)		–0.01 (–0.05 to 0.03)	
												5-year change in semantic fluency (-)		0.01 (–0.03 to 0.04)	
												5-year change in phonemic fluency (-)		0.00 (–0.01 to 0.03)	
Tzivian 2016a	HNR	Ruhr Areas, Germany	Cross sectional	2006–2008	3,085	64	Both	LUR	PM_{10} mass	27.7	Cognitive function	Global cognitive score (-)	mean difference	−0.15 (−0.26 to −0.04)	2.09 µg/m³
												Verbal fluency (-)		−0.03 (−0.07 to 0.01)	
												Labyrinth test (problem-solving/processing speed) (-)		−0.05 (−0.09 to −0.02)	
												Immediate recall (verbal memory) (-)		−0.02 (−0.05 to 0.01)	
												Delayed recall (verbal memory) (-)		−0.03 (−0.06 to 0.01)	
												Clock drawing test (dichotomous, abstraction/visual-spatial organization).	odds ratio (OR)	0.99 (0.90 to 1.08)	
									PM_{coarse} mass	10.13		Global cognitive score (-)	mean difference	−0.21 (−0.33 to −0.10)	1.84 µg/m³
												Verbal fluency (-)		−0.07 (−0.11 to −0.03)	
												Labyrinth test (problem-solving/processing speed) (-)		−0.05 (−0.09 to −0.01)	
												Immediate recall (verbal memory) (-)		−0.04 (−0.08 to −0.01)	
												Delayed recall (verbal memory) (+)		−0.04 (−0.08 to −0.01)	
												Clock drawing test (dichotomous, abstraction/visual-spatial organization).	odds ratio (OR)	0.97 (0.88 to 1.07)	

[a] Unit in the increment column.

[b] A negative direction (-) means that a lower score indicates poorer cognitive function; a positive direction (+) means that a higher score indicates poorer cognitive function. Ratio measures (RRs, ORs, IRRs) >1.0 indicate higher risk for the outcome.

Table 13A-5. Associations of indirect traffic measures with cognitive function and cognitive decline.

Reference	Study Name	Location	Study Design	Study period	Sample size	Mean age baseline (years)	Sex	Traffic measure	Outcome	Neuropsychological tests (direction[a])	Effect measure	Effect Estimate (95% CI)	Increment
Ranft 2009	SALIA	Ruhr Areas, Germany	Cross sectional	2007–2008	396	54–55	Female	Distance	Cognitive function	CERAD-Plus tests total scores (-)	mean difference	−3.8 (−7.8 to 0.1)	<50 vs. >50 m
										Stroop test, log-transformed score (-)		−5.1 (−8.2 to −2.0)	
										Sniffing test (-)		−1.3 (−2.4 to −0.2)	
Schikowski 2015	SALIA	Ruhr Areas, Germany	Cross sectional	2007–2009	789	55	Female	Density	Cognitive function	Global cognition; CERAD (-)	mean difference	−0.40 (−2.16 to 1.36)	26.7 thousand vehicle-km/day on major roads <100 m distance and >50,000 cars/day
										Global cognition: MMSE (-)		0.04 (−0.18 to 0.26)	
										Semantic memory: semantic fluency (-)		0.09 (−0.08 to 0.25)	
										Semantic memory: Boston naming test (-)		−0.03 (−0.24 to 0.17)	
										Semantic memory: phonetic fluency (-)		−0.07 (−0.27 to 0.13)	
										Episodic memory: word list learning (-)		−0.02 (−0.22 to 0.19)	
										Episodic memory: word list recall (-)		−0.02 (−0.22 to 0.17)	
										Constructional praxis: figure copying (-)		−0.10 (−0.35 to 0.14)	
										Constructional praxis: figure recall (-)		0.03 (−0.23 to 0.17)	
										Executive function: trail-making A (-)		0.08 (−0.10 to 0.26)	
										Executive function: trail-making B (-)		0.13 (−0.05 to 0.31)	
										Executive function: trail-making B/A (-)		0.07 (−0.11 to 0.25)	
Tzivian 2016a	HNR	Ruhr Areas, Germany	Cross sectional	2006–2008	3,085	64	Both	Density	Cognitive function	Global cognitive score (-)	mean difference	0.02 (−0.04 to 0.07)	13.5 x 100k vehicle-m/day <100m distance and >5,000 cars/day
										Verbal fluency (-)		0.01 (−0.02 to 0.03)	
										Labyrinth test (problem-solving/processing speed) (-)		0.01 (−0.02 to 0.04)	
										Delayed recall (verbal memory) (-)		−0.01 (−0.03 to 0.03)	
										Immediate recall (verbal memory) (-)		−0.01 (−0.03 to 0.03)	
										Clock drawing test (dichotomous, abstraction/visual-spatial organization)	odds ratio (OR)	1.03 (0.98 to 1.09)	

Wellenius 2012	MOBILIZE	Boston, Massachusetts, United States	Cohort	2005–2008	765	78.1	Both	Distance	Cognitive function	Low MMSE score (<25)	odds ratio (OR)	1.07 (0.84 to 1.36)	<100 vs. >1000 m
										Immediate recall: Hopkins Verbal Learning Test-Revised (HVLT-R) (-)	mean difference	−1.6 (−2.9 to −0.3)	
										Delayed recall: (HVLT-R) (-)		−1.1 (−1.9 to −0.3)	
										Recognition: HVLT-R) (-)		0.2 (−0.3 to 0.8)	
										Letter Fluency (-)		−1.5 (−4.7 to 1.8)	
										Category Fluency (-)		−0.8 (−1.9 to 0.3)	
										Clock-in-the-Box (-)		−0.1 (−0.4 to 0.2)	
										Trailmaking Test Part A (-)		7.4 (−2.2 to 16.9)	
										Trailmaking Test Part B (-)		15.2 (−1.6 to 32.0)	
										Trailmaking Test Delta(B-A) (-)		6.9 (−6.5 to 20.3)	

[a] A negative direction (-) means that a lower score indicates poorer cognitive function; a positive direction (+) means that a higher score indicates poorer cognitive function. Ratio measures (RRs, ORs, IRRs) >1.0 indicate higher risk for the outcome.

Appendix 13B Dementia and mild cognitive impairment

Table 13B-1. Key study characteristics of studies included in the narrative review for dementia and mild cognitive impairment – pollutants and indirect traffic measures (*N*=7).

Reference[a]	Study Name	Location	Study period	Sample size	Mean age baseline (years)	Exposure Assessment	Exposure window	Pollutant	Outcome	Outcome details
Carey 2018	CPRD	London, England	2005–2013	130,978	50–79[b]	Dispersion / CTM, Distance or density	One year average one year before baseline	Density, Distance, NO_2, $PM_{2.5}$ mass, $PM_{2.5}$ traffic	Dementia	Incident diagnosis of dementia from medical records
Cerza 2019	Rome Longitudinal Study	Rome, Italy	2001–2013	350,844	74.5	LUR, Distance or density	One year average at baseline using ESCAPE	Distance, NO_2, NO_x, EC. PM_{10} mass, PM_{coarse} mass, $PM_{2.5}$ mass	Dementia	First hospitalization for dementia from medical records
Chen 2017a	ONPHEC	Ontario, Canada	2001–2013	2,066,639	55–85[b]	LUR	5 year moving average with 2-year lag to follow-up	NO_2	Dementia	Dementia defined by hospital admission, physician claims or prescriptions
Chen 2017b	ONPHEC	Ontario, Canada	2001–2013	2,165,268	66.8	Distance or density	5 years before start of follow-up period	Distance	Dementia	Diagnosis of dementia or claim for medication related to dementia
Ilango 2019	CCHS	Ontario, Canada	1996–2013	34,391	59	LUR	3-year moving average with 5- year lag to follow-up	NO_2, $PM_{2.5}$ mass	Dementia	Hospital admission with diagnosis of dementia, 3 physician claims in 2 years, or prescription claim related to dementia
Oudin 2016	Betula	Umea, Sweden	1993–2010	1,806	55–85[b]	LUR	One year average at baseline	NO_x	Dementia	Diagnosis of dementia using medical records and assessed from cognitive test battery, MMSE and questionnaire
Tzivian 2016b	HNR	Ruhr Areas, Germany	2006–2008	2,050	45–75	LUR, Distance or density	Annual average using ESCAPE 2008-2009. Single test was administered in 2006-2008	Density, NO_2, NO_x, EC, PM_{10} mass, $PM_{2.5}$ mass, PM_{coarse} mass	MCI[c]	Low score on one of five HNR tests (immediate and delayed memory, abstraction, problem-solving speed, visual-spatial organization, verbal fluency) or self-reported cognitive decline in past 2 years

[a] All studies are cohort studies estimating incidence measures expressed by hazard ratios except for Tzivian 2016b which was cross sectional /cohort analysis and expressed as odds ratio. Sex is "both" in all studies.

[b] Age range at baseline (yrs).

[c] Mild Cognitive Impairment.

Table 13B-2. Associations of $PM_{2.5}$ mass with dementia and mild cognitive impairment.

Reference[a]	Study Name	Location	Study period	Sample size	Mean age baseline (years)	Exposure Assessment	Mean or median exposure[b]	Outcome	Effect Estimate (95% CI)	Increment
Carey 2018	CPRD	London, England	2005–2013	130,978	50–79	Dispersion / CTM	15.7	Dementia	1.07 (1.02–1.12)	0.95 μg/m^3
Cerza 2019	Rome Longitudinal Study	Rome, Italy	2001–2013	350,844	74.5	LUR	19.7	Dementia	0.99 (0.96–1.02)	5 μg/m^3
Ilango 2019	CCHS	Ontario, Canada	1996–2013	34,391	59	LUR	8.6	Dementia	1.29 (0.99–1.64)	10 μg/m^3
Tzivian 2016b	HNR	Ruhr Areas, Germany	2006–2008	2,050	45–75	LUR	18.4	MCI[c]	1.16 (1.05–1.27)	1.44 μg/m^3

[a] All studies are cohort studies estimating incidence measures expressed by hazard ratio's except for Tzivian 2016b which was cross sectional /cohort analysis and expressed as odds ratio. Sex is "both" in all studies.

[b] Unit in the increment column.

[c] Mild Cognitive Impairment.

Table 13B-3. Associations of EC with dementia and mild cognitive impairment.

Reference[a]	Study Name	Location	Study period	Sample size	Mean age baseline (years)	Exposure Assessment	Pollutant	Mean or median exposure[b]	Outcome	Effect Estimate (95% CI)	Increment
Cerza 2019	Rome Longitudinal Study	Rome, Italy	2001–2013	350,844	74.5	LUR	$PM_{2.5abs}$	2.76	Dementia	1.00 (0.98–1.03)	1 1×10^{-5}/m
Tzivian 2016b	HNR	Ruhr Areas, Germany	2006–2008	2,050	45–75	LUR	$PM_{2.5abs}$	1.58	MCI[c]	1.11 (1.03–1.19)	0.35 1×10^{-5}/m

[a] Cerza 2015 is a cohort study estimating incidence measures expressed by hazard ratios while Tzivian 2016b is cross sectional /cohort analysis expressed as odds ratio. Sex is "both" in all studies.

[b] Unit in the increment column.

[c] Mild Cognitive Impairment.

Table 13B-4. Associations of PM_{10}, PM_{coarse}, and PM components with dementia and mild cognitive impairment.

Reference[a]	Study Name	Location	Study period	Sample size	Mean age baseline (years)	Exposure Assessment	Pollutant	Mean or median exposure[b]	Outcome	Effect Estimate (95% CI)	Increment
Carey 2018	CPRD	London, England	2005–2013	130,978	50–79	Dispersion / CTM	$PM_{2.5}$ traffic	1.4	Dementia	1.08 (1.01, 1.16)	0.58 μg/m^3
Cerza 2019	Rome Longitudinal Study	Rome, Italy	2001–2013	350,844	74.5	LUR	PM_{10} mass	36.9	Dementia	1.00 (0.98, 1.03)	10 μg/m^3
							PM_{coarse} mass	17.4		0.98 (0.96, 1.00)	5 μg/m^3
Tzivian 2016b	HNR	Ruhr Areas, Germany	2006–2008	2,050	45–75	LUR	PM_{10} mass	27.7	MCI[c]	1.11 (0.99, 1.23)	2.09 μg/m^3
							PM_{coarse} mass	10.1		1.11 (0.98, 1.26)	1.00 μg/m^3

[a] All studies are cohort studies estimating incidence measures expressed by hazard ratios except for Tzivian 2016b which is cross-sectional analysis expressed as odds ratio. Sex is "both" in all studies.

[b] Unit in the increment column.

[c] Mild Cognitive Impairment.

Table 13B-5. Associations of indirect traffic measures with dementia and mild cognitive impairment.

Reference[a]	Study Name	Location	Study period	Sample size	Mean age baseline (years)	Traffic measure	Outcome	Effect Estimate (95% CI)	Increment
Carey 2018	CPRD	London, England	2005–2013	130,978	50–79	Density[b]	Dementia	1.10 (0.90–1.35)	>100,000 veh-km/yr <50 m vs. none within 100 m
								0.98 (0.83–1.15)	>100,000 veh-km/yr within 50-100 m vs. none within 100 m
								1.06 (0.95–1.19)	<100,000 veh-km/yr <50 m vs. none within 100 m
								1.01 (0.89–1.15)	<100,000 veh-km/yr within 50-100m vs. none within 100 m
						Distance		1.09 (0.94–1.26)	<50 vs. >250 m
								0.98 (0.84–1.13)	50-100 vs. >250 m
								1.05 (0.95–1.16)	100-250 vs. >250 m
Cerza 2019	Rome Longitudinal Study	Rome, Italy	2001–2013	350,844	74.5	Distance	Dementia	1.01 (0.97–1.06)	<50 vs. >300 m
								0.98 (0.93–1.02)	50-100 vs. >300 m
Chen 2017b	ONPHEC	Ontario, Canada	2001–2013	2,165,268	66.8	Distance	Dementia	1.07 (1.06–1.08)	<50 vs. >300 m
								1.04 (1.02–1.05)	50-100 vs. >300 m
Tzivian 2016b	HNR	Ruhr Areas, Germany	2006–2008	2,050	45–75	Density	MCI[c]	1.00 (0.94–1.07)	1 vehicle-km/day

[a] All studies are cohort studies estimating incidence measures expressed by hazard ratios except for Tzivian 2016b which is cross-sectional /cohort analysis expressed as odds ratio. Sex is "both" in all studies.

[b] Traffic volume unit is km driven by heavy vehicles per year. Reference is no heavy vehicle traffic within 100m.

[c] Mild Cognitive Impairment.

Appendix 13C Parkinson disease

Table 13C-1. Key study characteristics of studies included in the narrative review for Parkinson disease – pollutants and indirect traffic measures (*N*=6).

Reference	Study Name	Location	Study design	Study period	Sample size[a]	Mean age baseline (years)	Exposure Assessment	Exposure window	Pollutant	Incidence or prevalence	Outcome details
Cerza 2018	Rome Longitudinal Study	Rome, Italy	Cohort	2008–2013	1,008,253	63	LUR	One year average at baseline using ESCAPE	NO_2, NO_x, EC, PM_{10} mass, PM_{coarse} mass, $PM_{2.5}$ mass	Incidence	Use of hospital discharge data, or two pharmacy claims in one year
Chen 2017b	ONPHEC	Ontario, Canada	Cohort	2001–2013	2,165,268	66.8	Distance or density	5 years before start of follow-up period	Distance	Incidence	Use of hospital discharge data, physician service claims and prescription medication claims
Finkelstein 2007	THUA OHIP	Ontario, Canada	Case-control	1992–1999	52,986	14–92	Distance or density, LUR	Long-term average near end of follow-up	Distance, NO_2	Prevalence	Prescription for L-Dopa, or physicians' diagnosis
Ritz 2016	PASIDA	Multiple cities, Denmark	Case-control	1996–2009	3,496	62	Dispersion / CTM	Cumulative average	NO_2	Incidence	Medical records, including notes about the presence of 2 or more symptoms (resting tremor, bradykinesia, rigidity, and asymmetrical onset). The occurrence of the first cardinal (motor) symptom noted on the medical record or—if missing—the first known date of hospitalization/outpatient clinic visit due to PD was the reference date.
Shin 2018	ONPHEC	Ontario, Canada	Cohort	1996–2013	2,194,519	67	LUR	5-year moving average with a 2-year lag	NO_2	Incidence	Two physician claims within1-year, or prescription and physician claim within 6 months before or after the prescription
Toro 2019	Netherlands five hospitals	Multiple cities, The Netherlands	Case-control	2010–2012	1,290	53	LUR	Cumulative average using ESCAPE	NO_2, NO_x, EC, PM_{10} mass, PM_{coarse} mass, $PM_{2.5}$ mass	Incidence	Medical records. A neurologist reviewed the medical records of patients with a diagnosis of PD. Individuals were eligible as cases if they were initially diagnosed between January 2006 to December 2011.

[a] Sex is "both" in all studies.

Table 13C-2. Associations of PM mass with Parkinson disease.

Reference	Study Name	Location	Study design	Study period	Sample size[a]	Mean age baseline (years)	Exposure Assessment	Pollutant	Mean or median exposure[b]	Incidence or prevalence	Effect measure	Effect Estimate (95% CI)	Increment
Cerza 2018	Rome Longitudinal Study	Rome, Italy	Cohort	2008–2013	1,008,253	63	LUR	PM_{10} mass	36.7	Incidence	hazard ratio (HR)	0.98 (0.95–1.01)	10 µg/m^3
								PM_{coarse} mass	19.6			0.97 (0.95–1.00)	5 µg/m^3
								$PM_{2.5}$ mass	17.0			0.96 (0.92–1.00)	5 µg/m^3
Toro 2019	Netherlands five hospitals	Multiple cities, The Netherlands	Case-control	2010–2012	1,290	53	LUR	PM_{10} mass	31.9	Incidence	odds ratio (OR)	0.68 (0.15–3.1)	1 µg/m^3
								PM_{coarse} mass	10.3			0.47 (0.1–2.15)	5 µg/m^3
								$PM_{2.5}$ mass	21.6			0.8 (0.2–3.17)	5 µg/m^3

[a] Sex is "both" in all studies.

[b] Unit in the increment column.

Table 13C-3. Associations of EC with Parkinson disease.

Reference	Study Name	Location	Study design	Study period	Sample size[a]	Mean age baseline (years)	Exposure Assessment	Pollutant	Mean or median exposure[b]	Incidence or prevalence	Effect measure	Effect Estimate (95% CI)	Increment
Cerza 2018	Rome Longitudinal Study	Rome, Italy	Cohort	2008–2013	1,008,253	63	LUR	$PM_{2.5abs}$	2.71	Incidence	hazard ratio (HR)	0.94 (0.91–0.98)	1 1×10^{-5}/m
Toro 2019	Netherlands five hospitals	Multiple cities, The Netherlands	Case-control	2010–2012	1,290	53	LUR	$PM_{2.5abs}$	1.42	Incidence	odds ratio (OR)	0.77 (0.34–1.73)	1 1×10^{-5}/m

[a] Sex is "both" in all studies.

[b] Unit in the increment column.

Table 13C-4. Associations of indirect traffic measures with Parkinson disease.

Reference	Study Name	Location	Study design	Study period	Sample size[a]	Mean age baseline (years)	Traffic measure	Incidence or prevalence	Effect measure	Effect Estimate (95% CI)	Increment
Chen 2017b	ONPHEC	Ontario, Canada	Cohort	2001–2013	2,165,268	66.8	Distance	Incidence	hazard ratio (HR)	1.01 (0.98–1.04) 1.01 (0.97–1.05)	<50 vs. >300 m 50–100 vs. >300 m
Finkelstein 2007	THUA OHIP	Ontario, Canada	Case-control	1992–1999	52,986	14–92	Distance	Prevalence	odds ratio (OR)	1.03 (0.85–1.06)	<50 m. to major road or <100 m to highway vs. greater

[a] Sex is "both" in all studies.

Appendix 13D Further elaborations on limitations of evidence on TRAP and neurodegenerative outcomes

Dementia-related outcomes

Consistency of TRAP associations with dementia-related outcomes

The effect of TRAP exposure on dementia risk may be specific to effects on particular stages of etiology. Under some scenarios, stage-specific effects could result in associations of TRAP with some but not all dementia-related outcomes. The main text in Section 13.5.3 characterized two of these scenarios. In a third scenario, it may be that TRAP mainly influences a phase of accelerated cognitive decline that precedes death, a phenomenon called terminal decline (Karr et al. 2018; Wilson et al. 2020). Terminal decline appears to be only weakly tied to dementia pathologies and has been hypothesized to result from unspecified factors influencing impending mortality (Boyle et al. 2013; Karr et al. 2018; Wilson et al. 2020). Under this scenario where TRAP primarily affects terminal decline, TRAP would be adversely associated with dementia, especially in studies defining dementia according to acute or end-of-life events such as hospitalizations. TRAP would also be associated with cognitive decline in studies that measured cognitive function among persons near the end of life but not with decline or cognitive level before then. In the absence of cognitive assessments repeated over a long period, studies of cognitive decline cannot necessarily distinguish between "pre-terminal" and terminal decline. Studies of younger persons (e.g., < 65 years) probably involve few persons in terminal decline, but age is an imperfect proxy for decline stage, because illness, more than age, influences decline (Boyle et al. 2013; Wilson et al. 2020).

Dementia misclassification

To identify persons with dementia and the timing of their condition's onset, 5 studies of dementia in this review relied on data from the administration of and billing for health care in the community—encompassing data such a medical records, prescriptions, and insurance claims. A sixth study partially relied on these data. These approaches can broaden the reach of a study to populations that are often underrepresented in research and can result in very large sample sizes. But little is known about the validity of these approaches. What is known indicates that they have potential to bias the estimated effects of TRAP on dementia incidence.

Misclassification of dementia status in medical records and claims is common, and the accuracy of using these data for ascertaining dementia cases is generally much poorer than for ascertaining cases of severe acute conditions. There are several indications that persons with dementia may be grossly underrepresented as diagnosis-related events in administrative data. In one review, underdiagnosis in these data, which might involve missed or delayed diagnosis, often exceeded 50% (Lang et al. 2017). Some dementias may be misdiagnosed, reflecting rule-out diagnoses or diagnoses made during terminal decline at the end of life. This imperfect specificity contributes to low positive predictive values, such as the 56% PPV reported for a dementia diagnosis in U.S. Medicare claims (Taylor et al. 2009).

If dementia misclassification occurs non-differentially with respect to TRAP exposure, the ensuing bias on effect estimates would probably be toward the null. Rather, the concern is that misclassification of dementia status in these records may vary by TRAP exposure and produce a bias of indeterminate direction, possibly upward. Little is known about whether dementia status in administrative data is

differentially misclassified across levels of TRAP exposure. But such differential misclassification is plausible. Rates of dementia under-diagnosis vary by health status, as well as by race/ethnicity and other sociodemographic characteristics (Gianattasio et al. 2019; Power et al. 2020). In many settings, it is plausible that the same factors that predict the accuracy of dementia diagnosis also correlate with TRAP exposure (Hajat et al. 2015; Miranda et al. 2011; Tessum et al. 2021). Persons living in high-TRAP areas could have higher rates of over-diagnosis because their other TRAP-related health conditions prompt encounters with the medical system. Or persons in high-TRAP areas could have higher rates of underdiagnosis or be diagnosed later in the course of their condition. Additional spatially patterned determinants of misclassification might exist, as well, even in settings that provide universal health care for older adults or expansive socialized health care (Power et al. 2020; Rizzuto et al. 2018; Solomon et al. 2014; Taylor et al. 2009). Occasionally, researchers condition health effects analyses on factors that influence outcome misclassification (e.g., by including these factors as covariates in a regression model), for the express purpose of mitigating misclassification-related bias in the health effect estimate. Instead, this approach can induce new bias (Greenland and Robins 1985). The intuition is that conditioning succeeds in adjusting for confounding by creating strata of data within which baseline outcome risks are equivalent, irrespective of exposure. But conditioning according to a misclassification factor creates strata defined by their degree of outcome misclassification. The resulting effect estimate, weighted across strata, is not necessarily any closer to truth.

The studies of dementia and mild cognitive impairment implicitly or explicitly sought to measure incident disease. In the Rome Longitudinal Study, the outcome was defined as first hospitalization with a dementia diagnosis (Cerza et al. 2019). This measure likely captures newly onset cases and established cases that require hospitalization because they are sufficiently severe or involve acute comorbid conditions. Thus, estimates from these studies may mismeasure dementia onset and reflect the effects of air pollution on acute comorbid conditions (Phelan et al. 2012) or even the exacerbation of dementia symptoms. That said, the involvement of air pollution exposure in progression and symptom exacerbation is a worthwhile realm for future research.

Clearly, administrative data offer potential to conduct high-powered and detailed studies of TRAP and dementia risk but understanding this data's accuracy trails far behind its use. Offering direction toward the much-needed research toward that understanding are the aforementioned validation studies, along with a tradition of validation research on other outcomes such as stroke and heart failure.

Selection bias

Selection in studies of dementia-related outcomes entails two primary dimensions: who enters a study (e.g., via recruitment and enrollment or detection in an administrative database) and who continues participating over follow-up (e.g., by not dropping out or dying). Many studies of TRAP and dementia-related outcomes are inherently susceptible to selection bias, because (a) death or disability that limits study participation is common prior to the age at enrollment—affecting who enters a study—and over the course of follow-up—affecting attrition from drop-out or death; (b) cognitive status predicts study participation; and (c) it is reasonable to assume that higher exposure to TRAP, via its effects on morbidity and mortality, might influence participation as well (Weuve 2020). With these patterns at work, then studies of TRAP and dementia-related outcomes could suffer from collider bias, with the most highly exposed participants having better-than-expected cognitive status. Thus, we would expect an ensuing upward bias in effect estimates of TRAP on cognition and cognitive change and downward bias in corresponding estimates for dementia—i.e., less adverse overall. The magnitude of the ensuing underestimate of TRAP's adverse effect depends on the interplay of TRAP and cognitive status in

influencing participation, whether at the point of enrollment or continuation, and can be especially severe in settings with high mortality (Mayeda et al. 2016, 2018; Weisskopf et al. 2015). This bias is a concern especially for studies restricted to very old persons (who must have survived to be eligible) or, by that logic, studies of incident dementia and studies of cognitive decline that follow participants to very advanced ages.

Although this bias is unlikely to have accounted for many of the adverse dementia findings, it is possible that it may have been present in the studies of cognitive change, an outcome that hinges on continued follow-up. Some studies in this review of dementia-related outcomes provided information on post-enrollment attrition from their cohorts, along with correlates of attrition. None of the studies in this review of dementia-related outcomes used methods to adjust for differential loss to follow-up. Still, use of such methods is becoming more common in etiologic studies of air pollution, dementia-related outcomes, and, recently, the etiologic relation between the two (Kulick et al. 2020; Paul et al. 2020; Power et al. 2018).

Statistical adjustment

Age and educational attainment are typically important sources of confounding in analyses of TRAP in relation to dementia-related outcomes. Advancing age is among the strongest, most consistent, and prevalent determinant of dementia risk, and all studies of dementia-related outcomes adjusted for age, typically as a continuous covariate in multivariable-adjusted models. Higher level of attained education is associated with lower dementia risk and higher scores on cognitive tests, and TRAP exposure often varies by educational level (Hajat et al. 2015). Most studies adjusted for measures of individual-level educational attainment, although 3 studies of dementia did not (Carey et al. 2018; Chen et al. 2017a, 2017b). In lieu of this adjustment were adjustments for area-level SES. There were also studies that adjusted for additional or alternative SES indicators and health-related behaviors (e.g., smoking, physical activity, alcohol consumption). Late-life body mass index was included as a covariate in several analyses. This not ideal, because, on average, persons who develop dementia lose more weight (or gain less weight) than their peers, over the course of many years prior to diagnosis, suggesting that incipient disease may influence body mass (Buchman et al. 2005; Gustafson et al. 2012; Hughes et al. 2009; Stewart et al. 2005).

Some studies, in primary or secondary analyses, also adjusted for putative mediators of the effect of TRAP on dementia risk (e.g., cardiovascular conditions, diabetes, depressive symptoms). The rationale for these adjustments was to evaluate mediation by these variables of any TRAP effects on the dementia-related outcome. This approach involves two major challenges. First, inferring mediation using the “add-one-in” approach rests on critical assumptions being met (Kaufman et al. 2004; Valeri and Vanderweele 2013). More important, even if these assumptions are met, it may be difficult to establish, using the data at hand, the temporal order of exposure, mediator, and dementia-related outcome, especially that the mediator preceded the onset of the outcome.

Finally, when cognitive test performance is strongly affected by SES, which can entail experience with testing, the estimated effect of TRAP on cognitive function can be confounded if SES tracks strongly with TRAP exposure. The resulting bias makes TRAP appear more adverse than it truly is, but the direction depends on the co-patterning of TRAP and SES in the study population. This bias similarly may exaggerate the estimated adverse association of TRAP with dementia if dementia is defined using a test score cut-off or without regard to previous level of function. Estimates of the adverse association of TRAP on cognitive decline may be less susceptible to this particular bias, so long as non-dementing factors (especially socioeconomic position) that affect participants’ testing ability stay the same or occur

randomly. Although many studies of cognitive decline routinely omit adjustments for determinants of cognitive change (e.g., via cross-products with time in study), it is not clear whether this is consequential.

Parkinson disease

Parkinson disease misclassification

To classify persons with and without Parkinson disease, all six studies of TRAP and Parkinson disease relied on health care data, which may be susceptible to misclassification. In community healthcare settings (i.e., in the course of regular medical care outside of investigative settings), misdiagnosis and delays in diagnosis are not uncommon (Breen et al. 2013; Rizzo et al. 2016; Schrag et al. 2018; Wan et al. 2019; Wermuth et al. 2012). Increasing availability of electronic claims, outpatient and hospital diagnosis codes, and prescription records has fueled the use of these data to identify persons with Parkinson disease in epidemiologic studies. The accuracy of these records, measured against the full medical record, varies, with a review finding wide-ranging positive predictive values (36-89%) of individual sources (e.g., hospital discharge only) that improved in magnitude and consistency when sources were used in algorithmic combination (>82%) (Harding et al. 2019). The "gold standard" in these validation studies was the medical record, which is as accurate as the medical system it records. According to a systematic review, Parkinson disease diagnoses made in community healthcare settings had about 80% accuracy against a pathology-based gold standard, higher for movement disorder specialists and lower for non-specialists (Rizzo et al. 2016). Most of the studies in our review relied solely on some combination of diagnostic codes and prescription data to identify Parkinson disease. One notable exception was the PASIDA study, in which researchers first identified potential cases from a roster of patients with hospital or outpatient diagnostic codes indicative of Parkinson disease and then perused these patients' medical records to confirm a diagnosis of idiopathic Parkinson disease, as opposed to other conditions that manifest similar symptoms, which resulted in the exclusion of about 18% of candidate cases (Ritz et al. 2016; Wermuth et al. 2012), a correction consistent with the aforementioned review of clinical diagnostic accuracy. Using Parkinsonism (the result of any of 6 conditions) instead of Parkinson disease as the outcome, even when persons are accurately classified with Parkinsonism, could introduce misclassification if inference to Parkinson disease is the goal. Except for the PASIDA study and Rome Longitudinal Study (Cerza et al. 2018; Ritz et al. 2016), all other studies used case definitions that explicitly or implicitly included persons with Parkinsonism but not necessarily Parkinson disease.

Selection bias

The average age at Parkinson disease onset (i.e., when symptoms are sufficient to meet diagnostic criteria) appears to be about a decade younger than that of dementia. This younger onset age could make studies of TRAP and Parkinson disease more resistant to bias from differential survival. Nonetheless, most studies in this review included a large proportion of cases (>20%) whose Parkinson disease onset occurred at age 75 or older. As with studies of TRAP and dementia, any differential survival in studies of Parkinson disease would have likely biased estimated effects of TRAP downward (to a less positive or more inverse estimate). This assumes that TRAP exposure accelerates morbidity and mortality and that unmeasured determinants of Parkinson disease reduce survival and participation. As suggested by research on cancer and Parkinson disease, where a similar bias was suspected (Cui et al. 2019), it is not clear that such bias could fully account for the inverse associations of TRAP with Parkinson disease reported by some studies in this review.

Statistical adjustment

Third, an important source of residual confounding in studies of TRAP and Parkinson disease may be smoking history, which is which is strongly and inversely associated with Parkinson disease, and this information was only available in one study (Ritz et al. 2016). Smoking is consistently and strongly inversely associated with Parkinson disease risk (Chen and Ritz 2018; Gallo et al. 2019; Ritz et al. 2007). The reasons for this association remain unresolved (Chen and Ritz 2018). So long as the association of smoking with Parkinson disease risk is not entirely attributable to the effects of prodromal Parkinson disease, then, given its magnitude, it is important to measure and adjust for smoking history in studies of TRAP and Parkinson disease. The direction of bias in the association caused by confounding by smoking hinges on how smoking and TRAP are jointly distributed in the study population. If smoking and TRAP exposure are positively correlated, as in some populations (e.g., Shaffer et al. 2021; Weuve et al. 2016), the association is expected to be biased downward. This could potentially explain upward shifts in estimates with adjustment for smoking history (e.g., Ritz et al. 2016) and the small inverse associations reported by some studies with minimal smoking adjustment (e.g., Cerza et al. 2018). Nonetheless, without further information about the distribution of smoking and TRAP in these studies, it is difficult to infer the influence of confounding by smoking on their associations, particularly as the relationship between smoking and TRAP may vary by region, time, and dimension of smoking (e.g., dose, duration, time since quitting) (e.g., Aaron et al. 2019; Cheng and Wang 2020). Parkinson disease risk does not consistently appear to decrease along a gradient of increasing SES (e.g., Caslake et al. 2013; Yang et al. 2016), although this could reflect complex interplay of SES with key Parkinson disease risk factors such as smoking and physical activity.

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