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Health Effects of Ultrafine Particles

Systematic literature search and the potential transferability of the results to the German setting

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Health Effects of Ultrafine Particles

Systematic literature search and the potential transferability of the results to the German setting

by

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Annexes

- Part I: Literature search, used databases, selection process of the references, list of studies with UFP health effects published after the search period, indicators to describe and evaluate UFP-studies.
- Part II: Tables on short- and long-term health effects in the studies with co-pollutant effect estimates and quality aspects of the studies.

Part I

1. HEI search strategy

Our search strategy is based on the previous systematic search by the HEI (2013), which was conducted on 09.05.2011 in Web of Science and MEDLINE via Pubmed. The search was complemented extensively through hand researches in previous reviews (e.g. US PM ISA 2009).

- Search in the Web of Science on 09.05.2011
    - 966 references identified by the following search strategy:
        - Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CCR-EXPANDED, IC Timespan=1900-2011
        - # 12 966 #11 AND #10
        - # 11 >100,000 #8 OR #7
        - # 10 2,996 #9 AND #6
        - # 9 >100,000 #5 OR #4 OR #3 OR #2 OR #1
        - # 8 >100,000 Topic=(epidemiology)
        - # 7 >100,000 Topic=(health)
        - # 6 40,369 Topic=(air pollution)
        - # 5 >100,000 Topic=(surface area)
        - # 4 17,045 Topic=(number count)
        - # 3 76,211 Topic=(number concentration)
        - # 2 1,398 Topic=(particle count)
        - # 1 14,632 Topic=(ultrafine)
        - [search was rerun on 9/19/2011 – search step #12 found 1475 refs, but only 2 additional pubs from summer 2011 looked relevant for epi section]
    - 779 unique refs added (records 1673-2638)
- Searched PubMed on 5/9/2011
    - 926 refs found using the same search structure as for Web of Science:
        - #12 Search #11 AND #10 926
        - #11 Search #8 OR #7 3086579
        - #10 Search #9 AND #6 1906

  - #9 Search #1 OR #2 OR #3 OR #4 OR #5 212253
  - #8 Search epidemiology 1366933
  - #7 Search health 2111539
  - #6 Search air pollution 44525
  - #5 Search surface area 86295
  - #4 Search number count 45896
  - #3 Search number concentration 84177
  - #2 Search particle count 1472
  - #1 Search ultrafine 1687
- 695 unique refs added (records 2639-3564)

- Hand searches (including PM Integrated Science Assessment):

  - 417 references (originating from Particulate Matter – Integrated Science Assessment) (PM ISA) 2009: 281)

Exclusion criteria

- Articles focused on nanotechnology and workplace engineered NP exposure
- Indoor allergen papers
- In vivo and in vitro and human controlled exposure articles
- Articles with no particle count or size measurements (e.g., studies of traffic using only distance to roadway measures)
- Excluded articles where smallest size fraction examined was PM1 (e.g., Slaughter 2005)

2. LUDOK search strategy

Aufnahmekriterien sind u. a.: Epidemiologische und experimentelle Originalarbeiten über die Auswirkungen der „klassischen“ Aussenluftschadstoffe auf Menschen, sowie von weiteren Schadstoffen, die via Luft auf die Allgemeinbevölkerung einwirken (d. h. keine alleinig arbeitsmedizinisch relevanten Stoffe), inkl. Metaanalysen und methodische Arbeiten zu diesem Zusammenhang.

Suchstrategien in LUDOK:

- Sprache: en, fr, de, it (für dieses Projekt wurden nur Artikel in Deutsch und Englisch genutzt)
- Zeitraum: seit Beginn der Lufthygieneforschung bis heute (ältester Artikel von 1929, ca. 20 Artikel aus der Zeit vor 1971)
- Handsuche in relevanten Fachzeitschriften und allgemein wichtigen Journals über wöchentliche Alerts (s. unten)
- Datenbanken:
  - PubMed: Dauerrecherche mit gleich bleibender, sehr breiter Formulierung (monatlich)
    - Suchtermini: “Air Pollutants/adverse effects” [Mesh] OR “Air Pollution/adverse effects” [Mesh] OR “Air Pollutants” [Pharmacological Action][1] OR “Environmental Exposure/adverse effects” [Mesh] OR “air pollutants” OR “air pollution” OR “air pollutant”
  - EMBASE: Auf eine Dauerrecherche wurde nach einem Probelauf von 2,5 Monaten verzichtet. Der Zusatzaufwand steht in keinem Verhältnis zum Ergebnis: Ein Teil der wichtigen Papers wird bereits über die PubMed-Suche gefunden. Die Handsuche wird auf die wichtigsten Zeitschriften, die via EMBASE erfasst werden, erweitert. Dies sollte die EMBASE-Suche ersetzen.
- Referenzlisten von Publikationen (Originalarbeiten und Reviews), Bibliographien
- Hinweise aus verschiedenen Quellen: Swiss TPH-intern, BAFU, WHO, Mitteilung anderer Forschungsteams.

[1] Bringt keine zusätzlichen Treffer

Regelmäßige Handsuche in folgenden Zeitschriften

Tabelle 1: Regelmäßige Handsuchen

Name	Art	Erscheinungskadenz	ISSN-Nr.
Air Quality Atmosphere and Health – Air Qual Atmos Health	Alert	vierteljährlich	1873-9318 1873-9326
American Journal of Epidemiology – Am J Epidemiology	Alert	PubMed 2/Monat	0002-9262 1476-6256
American Thoracic Society: e.g. American Journal of Respiratory and Critical Care Medicine- Am J Respir Crit Care Med	Alert Search query	wöchentlich	1073-449x 1535-4970
Asian Pacific Journal of tropical Biomedicine	Alert	monatlich	
Atmospheric Environment	Alert	monatlich	1352-2310
Environment International	Alert	monatlich	0160-4120 1873-6750
Environmental Health – Environ Health	Alert	Keine Angaben Wöchentlich?	1476-069x
Environmental Health Perspectives – Environ Health Perspect	Alert	Alle 3 Wochen 17/Jahr	0091-6765 1551-9924
Environmental Research – Environ Res	Alert	wöchentlich	0013-9351 1096-0953
Epidemiology – Epidemiol	Alert Etoc?	Alle 2 Monate	1531-5487 1044-3983
European Respiratory Journal – Eur Respir J	Alert	Monatlich	0903-1936 1399-3003
Inhalation Toxicology – Inhal Toxicol	Alert HTML	Alle 3-4 Wochen 14/Jahr	0895-8378 1091-7691
International Journal of Epidemiology – Int J Epidemiol	Alert	monatlich	
Journal of Air & Waste Management Association	Alert	monatlich	1096-2247
Journal of Environmental Protection	Alert	1/Monat	
Journal of Exposure Science and Environmental Epidemiology – J Expo Sci Environ Epidemiol	Alert	Alle 2 Monate	1559-0631 1559-064x
Lancet Respiratory Medicine	Alert	wöchentlich	
Occupational and Environmental Medicine – Occup Environ Med	Alert Etoc	monatlich	1351-0711 1470-7926
Science of the Total Environment – Sci Total Enviro	Alert	wöchentlich	0048-9697 1879-1026

Name	Art	Erscheinungskadenz	ISSN
Lancet	Alert	Weekly	0140-6736 1474-547x
Journal of the American Medical Association – JAMA	Alert	Weekly	0098-7484 1538-3598
British Medical Journal – BMJ	Alert	Weekly	0959-8138 1756-1833
New England Journal of Medicine – N Eng J Med	Alert	Weekly	0028-4793 1533-4406
Swiss Medical Weekly – Swiss Med Wkly	Alert	monatlich	1424-7860 1424-3997

Einschlusskriterien LUDOK

Es werden vor allem Originalarbeiten eingeschlossen, die für die Schweiz bzw. den europäischen Kontext oder das Verständnis von (weltweiten) Belastungs-Wirkungsbeziehungen relevant sind und sich mit Wirkungen von Schadstoffen befassen, welche in der Luftreinhalteverordnung reguliert werden bzw. für die eine Regulierung diskutiert werden. Die Literatur wird systematisch gesucht, allerdings werden nur die in diesem Kontext relevanten Studien in die Datenbank aufgenommen.

Bei Zeitreihenstudien ist man dazu übergegangen, nur noch Studien aufzunehmen, wenn sie neue Zielgrössen untersuchen oder wenn sie ein Multi-pollutant-Modell rechnen.

Tierstudien sind dann interessant, wenn der Expositionspfad inhalativ (keine Instillation, keine Aufnahme durch die Nahrung) erfolgt und die Expositionsdauer langfristig ist, also langfristige Folgen untersucht werden.

3. UKD search strategy in MEDLINE

Date: 11.05.2017

Languages: German, English;

Search period: 01.01.2011 – 11.05.2017

Since our search was based on the HEI-review, we searched from 01.01.2011. The search strategy was developed in collaboration with the project team and in accordance with the UBA.

	Suchwort	Field-Tag	Treffer
#1	"Particulate matter"	[All Fields]	9.159
#2	"Environmental exposure"	[All Fields]	16.540
#3	"Air Pollutants"	[All Fields]	24.235
#4	„Air Pollution"	[All Fields]	13.120
#5	"Air pollutant"	[All Fields]	761
#6	"Air Pollutants/adverse effects"	[Mesh]	4.018
#7	"Air Pollution/adverse effects"	[Mesh]	3.654
#8	"Environmental Exposure/adverse effects"	[Mesh]	11.065
#9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8		50.395
#10	"Surface area"	[All Fields]	22929
#11	"Ultrafine"	[All Fields]	1816
#12	"Ultrafine particle"	[All Fields]	174
#13	"Ultrafine particles"	[All Fields]	540
#14	"Nano particle"	[All Fields]	247
#15	"Nano particles"	[All Fields]	779
#16	Nanoparticle	[All Fields]	28.010
#17	Nanoparticles	[All Fields]	90.587
#18	$PM_{0.1}$	[All Fields]	24
#19	$PM_{0.25}$	[All Fields]	6
#20	PNC	[All Fields]	417
#21	"Particle number"	[All Fields]	813
#22	"Accumulation mode"	[All Fields]	95
#23	"Aitken mode"	[All Fields]	10
#24	Submicron*	[All Fields]	1.542
#25	#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24		127.172
#26	health	[All Fields]	1.294.298
#27	epidemiology	[All Fields]	633.487

#28	epidemiological	[All Fields]	285.652
#29	epidemiologic	[All Fields]	525.623
#30	#26 OR #27 OR #28 OR #29		1.737.258
#31	**#9 AND #25 AND #30**		**1.100**

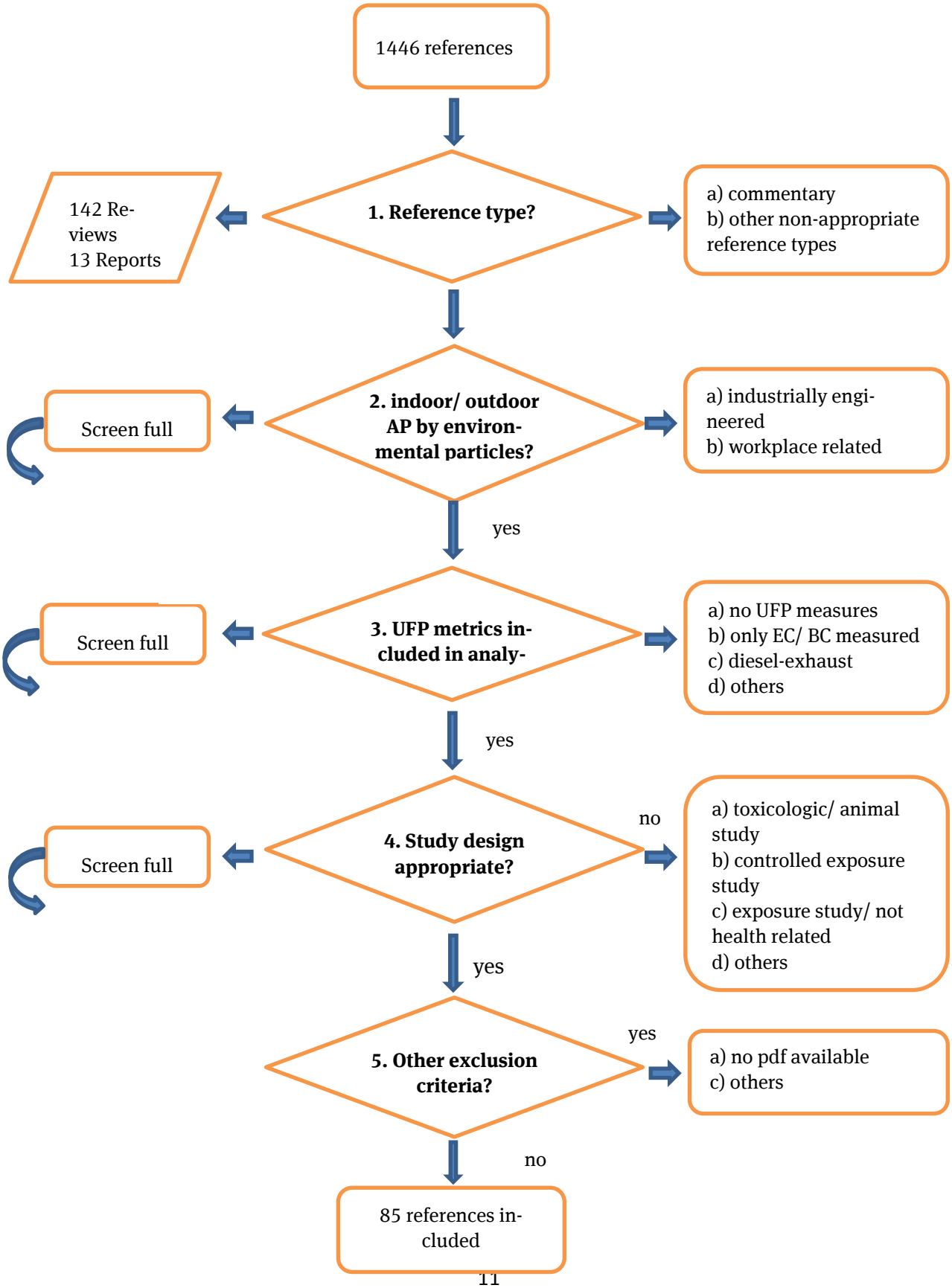
Additional search strategy using specific health outcomes (based on a template by the UBA)

	Suchwort	Field-Tag	Treffer
#1	"Particulate matter"	[All Fields]	9.159
#2	"Environmental exposure"	[All Fields]	16.540
#3	"Air Pollutants"	[All Fields]	24.235
#4	„Air Pollution"	[All Fields]	13.120
#5	"Air pollutant"	[All Fields]	761
#6	"Air Pollutants/adverse effects"	[Mesh]	4.018
#7	"Air Pollution/adverse effects"	[Mesh]	3.654
#8	"Environmental Exposure/adverse effects"	[Mesh]	11.065
#9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8		50.395
#10	"Surface area"	[All Fields]	22.929
#11	"Ultrafine"	[All Fields]	1816
#12	"Ultrafine particle"	[All Fields]	174
#13	"Ultrafine particles"	[All Fields]	540
#14	"Nano particle"	[All Fields]	247
#15	"Nano particles"	[All Fields]	779
#16	Nanoparticle	[All Fields]	28.010
#17	Nanoparticles	[All Fields]	90.587
#18	$PM_{0.1}$	[All Fields]	24
#19	$PM_{0.25}$	[All Fields]	6
#20	PNC	[All Fields]	417
#21	"Particle number"	[All Fields]	813
#22	"Accumulation mode"	[All Fields]	95
#23	"Aitken mode"	[All Fields]	10
#24	Submicron*	[All Fields]	1.542
#25	#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24		127.172
#26	Cardiovascular	[All Fields]	361.048
#27	vascular	[All Fields]	266.626
#28	cardiopulmonar*	[All Fields]	20.641

#29	ischaemic	[All Fields]	65.541
#30	ischemic	[All Fields]	90.058
#31	“myocardial infarction”	[All Fields]	49.221
#32	“heart attack”	[All Fields]	1.137
#33	“Cardiac infarction”	[All Fields]	84
#34	infarction	[All Fields]	63.263
#35	stroke	[All Fields]	99.768
#36	respirator*	[All Fields]	142.108
#37	pulmonar*	[All Fields]	145.534
#38	lung	[All Fields]	190.267
#39	asthma	[All Fields]	40.422
#40	copd	[All Fields]	25.258
#41	cancer	[All Fields]	918.403
#42	carcinoma	[All Fields]	209.814
#43	carcinogen*	[All Fields]	52.748
#44	malignan*	[All Fields]	141.485
#45	neoplas*	[All Fields]	570.667
#46	tumor	[All Fields]	825.207
#47	infectio*	[All Fields]	521.702
#48	disease	[All Fields]	1.146.966
#49	chronic inflammat*	[All Fields]	20.365
#50	systemic inflammat*	[All Fields]	12.404
#51	inflammat*	[All Fields]	326.167
#52	hospitaliz*	[All Fields]	72.874
#53	hospitalis*	[All Fields]	9.680
#54	“hospital admission”	[All Fields]	7.569
#55	emergency	[All Fields]	116.010
#56	mortality	[All Fields]	339.535
#57	death	[All Fields]	225.298
#58	depression	[All Fields]	111.407
#59	depressive	[All Fields]	47.920
#60	neurodegenerati*	[All Fields]	51.171
#61	alzheimer's	[All Fields]	50.714
#62	alzheimer*	[All Fields]	52.971
#63	parkinson's	[All Fields]	34.364
#64	parkinson*	[All Fields]	38.799

#65	dementia	[All Fields]	55.584
#66	diabetic	[All Fields]	64.131
#67	diabetes	[All Fields]	202.543
#68	metabolic	[All Fields]	175.842
#69	“low birth weight”	[All Fields]	9.703
#70	“low birthweight”	[All Fields]	1.476
#71	“preterm birth”	[All Fields]	6.737
#72	“premature birth”	[All Fields]	6.581
#73	“preterm delivery”	[All Fields]	3.086
#74	“premature delivery”	[All Fields]	438
#75	“premature infant”	[All Fields]	11.006
#76	“premature baby”	[All Fields]	76
#77	stillbirth	[All Fields]	3.267
#78	“dead birth”	[All Fields]	0
#79	stillborn	[All Fields]	572
#80	“immune system”	[All Fields]	37.177
#81	allergi*	[All Fields]	30.540
#82	#26 OR #27 OR #28 OR #29 ….#81		3.203.196
#83	**#9 AND #25 AND #82**		993

4. Flowchart on the selection of the studies



5. Repeated search in MEDLINE on 23.02.2018 in MEDLINE

Lucht S, Hennig F, Matthiessen C, Ohlwein S, Icks A, Moebus S, Jöckel K-H, Jakobs H, Hoffmann B. (in press). Air pollution and glucose metabolism: An analysis in non-diabetic participants of the Heinz Nixdorf Recall study. Accepted by Environ Health Perspect (in press, not yet indexed in MEDLINE).

Hennig F, Quass U, Hellack B, Küpper M, Kuhlbusch T, Stafoggia M, Hoffmann B. Ultrafine and Fine Particle Number and Surface Area Concentrations and Daily Cause-Specific Mortality in the Ruhr Area, Germany, 2009–2014. Environ Health Perspect. 2018; 126(2):1–10.; DOI:10.1289/EHP2054 (not yet indexed in MEDLINE).

Pilz V, Wolf K, Breitner S, Rückerl R, Koenig W, Rathmann W, Cyrys J, Peters A, Schneider A; KORA-Study group. C-reactive protein (CRP) and long-term air pollution with a focus on ultrafine particles. Int J Hyg Environ Health. 2018 Jan 31. pii: S1438-4639(17)30490-X. doi: 10.1016/j.ijheh.2018.01.016. [Epub ahead of print] PubMed PMID: 29428699.

Liu JY, Hsiao TC, Lee KY, Chuang HC, Cheng TJ, Chuang KJ. Association of ultrafine particles with cardiopulmonary health among adult subjects in the urban areas of northern Taiwan. Sci Total Environ. 2018 Jan 30;627:211-215. doi:10.1016/j.scitotenv.2018.01.218. [Epub ahead of print] PubMed PMID: 29426143.

Krauskopf J, Caiment F, van Veldhoven K, Chadeau-Hyam M, Sinharay R, Chung KF, Cullinan P, Collins P, Barratt B, Kelly FJ, Vermeulen R, Vineis P, de Kok TM, Kleinjans JC. The human circulating miRNome reflects multiple organ disease risks in association with short-term exposure to traffic-related air pollution. Environ Int. 2018 Jan 27;113:26-34. doi: 10.1016/j.envint.2018.01.014. [Epub ahead of print] PubMed PMID: 29421404.

Bai L, Chen H, Hatzopoulou M, Jerrett M, Kwong JC, Burnett RT, van Donkelaar A, Copes R, Martin RV, van Ryswyk K, Lu H, Kopp A, Weichenthal S. Exposure to Ambient Ultrafine Particles and Nitrogen Dioxide and Incident Hypertension and Diabetes. Epidemiology. 2018 Jan 9. doi: 10.1097/EDE.0000000000000798. [Epub ahead of print] PubMed PMID: 29319630.

Sinharay R, Gong J, Barratt B, Ohman-Strickland P, Ernst S, Kelly FJ, Zhang JJ, Collins P, Cullinan P, Chung KF. Respiratory and cardiovascular responses to walking down a traffic-polluted road compared with walking in a traffic-free area in participants aged 60 years and older with chronic lung or heart disease and age-matched healthy controls: a randomised, crossover study. Lancet. 2018 Jan 27;391(10118):339-349. doi: 10.1016/S0140-6736(17)32643-0. Epub 2017 Dec 5. Erratum in: Lancet. 2018 Jan 27;391(10118):308. PubMed PMID: 29221643; PubMed
Central PMCID: PMC5803182.

Forns J, Dadvand P, Esnaola M, Alvarez-Pedrerol M, López-Vicente M, Garcia-Esteban R, Cirach M, Basagaña X, Guxens M, Sunyer J. Longitudinal association between air pollution exposure at school

and cognitive development in school children over a period of 3.5 years. Environ Res. 2017 Nov;159:416-421. doi: 10.1016/j.envres.2017.08.031. Epub 2017 Sep 1. PubMed PMID: 28858754.

Endes S, Schaffner E, Caviezel S, Dratva J, Stolz D, Schindler C, Künzli N, Schmidt-Trucksäss A, Probst-Hensch N. Is physical activity a modifier of the association between air pollution and arterial stiffness in older adults: The SAPALDIA cohort study. Int J Hyg Environ Health. 2017 Aug;220(6):1030-1038. doi: 10.1016/j.ijheh.2017.06.001. Epub 2017 Jun 13. PubMed PMID: 28629640.

Goldberg MS, Labrèche F, Weichenthal S, Lavigne E, Valois MF, Hatzopoulou M, Van Ryswyk K, Shekarrizfard M, Villeneuve PJ, Crouse D, Parent MÉ. The association between the incidence of postmenopausal breast cancer and
concentrations at street-level of nitrogen dioxide and ultrafine particles. Environ Res. 2017 Oct;158:7-15. doi: 10.1016/j.envres.2017.05.038. Epub 2017 Jun 5. PubMed PMID: 28595043.

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Bell G, Mora S, Greenland P, Tsai M, Gill E, Kaufman JD. Association of Air Pollution Exposures with High-Density Lipoprotein Cholesterol and Particle Number: The Multi-Ethnic Study of Atherosclerosis. Arterioscler Thromb Vasc Biol.
2017 May;37(5):976-982. doi: 10.1161/ATVBAHA.116.308193. Epub 2017 Apr 13. PubMed PMID: 28408373; PubMed Central PMCID: PMC5407952.

Weichenthal S, Lavigne E, Valois MF, Hatzopoulou M, Van Ryswyk K, Shekarrizfard M, Villeneuve PJ, Goldberg MS, Parent ME. Spatial variations in ambient ultrafine particle concentrations and the risk of incident prostate cancer: A case-control study. Environ Res. 2017 Jul;156:374-380. doi: 10.1016/j.envres.2017.03.035. Epub 2017 Apr 10. PubMed PMID: 28395241.

6. Indicators to describe and evaluate UFP studies

a) General Study Information

1. **Reference** [author et al. (year)]

   _____
   (free text)

   Example: Lane et al. (2016)

Source: Custom-made

2. **Link to PubMed** (Endnote reference below abstract)

   _____
   (free text)

Source: Custom-made

3. **Was the research question or objective in this paper clearly stated?** *Did the authors describe their goal in conducting this research? Is it easy to understand what they were looking to find? This issue is important for any scientific paper of any type. Higher quality scientific research explicitly defines a research question.*

   a) Yes
   b) No
   c) Not applicable

Source: Modified after QAT (for Observational Cohort and Cross-Sectional studies) **Question 1** –possible answer categories .

4. **What is the location of the study?** *[City, Country]*

_____

(free text)

Example: Copenhagen, Denmark

Source: Custom made

5. **Which world region is the country of the study assigned?**
   a) Africa
   b) North America
   c) South America
   d) Western Europe
   e) Eastern Europe
   f) South-East Asia
   g) Western Pacific
   h) Multiple Regions

Source: http://www.who.int/about/regions/en/

6. **What is the study name/ project abbreviation?** (e.g., ESCAPE)

_____

(free text)

   a) Not applicable
   b) Not reported/ reference given
   c) Not reported/ no reference given

-> *Use abbreviation + "study", e.g., ESCAPE study*

Source: Custom-made

7. **What is the cohort name?**

_____

(free text)

d) Not applicable
e) Not reported/ reference given
f) Not reported/ no reference given

-> *Use abbreviation + "cohort", e.g., SAPALDIA cohort*

Source: Custom-made

8. What was the study design?

a) Cohort	Long-term outcome
b) Case-control	
c) Case-crossover	
d) Cross-sectional	
e) Panel (cross-sectional)	Short-/Medium-Term
f) Panel (repeated measures)	Short-/Medium-Term
g) Scripted exposures	Particip. is assigned to prespecified expo, for example a specific bike route through a city
h) Time-series	
i) Other	

-> No free text answers allowed, if unclear state "Other".

Source: Custom-made

9. If other study design used, specify/Further details on study design, e.g., repeated measures (in cohort). Otherwise, leave free.

_____
(free text)

a) Not determinable
b) Not reported

Source: Custom-made

10. What was the time horizon of the study? (Filter question)

a) Short-term (hours to days)
b) Medium-term (weeks)
c) Long-term (months to years)
d) Combination of Short- and Long-term
e) Not reported

Source: Custom-made

11. Was it a multicenter-study?

a) Yes
b) No

Source: Custom-made

b) Specific aspects of study design

12. **Was the study population clearly specified and defined?** *Did the authors describe the group of people from which the study participants were selected or recruited, using demographics, location, and time period? If you were to conduct this study again, would you know who to recruit, from where, and from what time period? Is the cohort population free of the outcomes of interest at the time they were recruited? An example would be men over 40 years old with type 2 diabetes who began seeking medical care at Phoenix Good Samaritan Hospital between January 1, 1990 and December 31, 1994. In this example, the population is clearly described as: (1) who (men over 40 years old with type 2 diabetes); (2) where (Phoenix Good Samaritan Hospital); and (3) when (between January 1, 1990 and December 31, 1994). Another example is women ages 34 to 59 years of age in 1980 who were in the nursing profession and had no known coronary disease, stroke, cancer, hypercholesterolemia, or diabetes, and were recruited from the 11 most populous States, with contact information obtained from State nursing boards. In cohort studies, it is crucial that the population at baseline is free of the outcome of interest. For example, the nurses' population above would be an appropriate group in which to study incident coronary disease. You may need to look at prior papers on methods in order to make the assessment for this question. Those papers are usually in the reference list.*

a) Yes

b) Not specified/ reference given
c) Not specified/ no reference given
d) Not applicable

Source: Modified after **Question 2 of QAT** (Cohort and cross-sectional studies), modified answer categories.

13. **What was the sample size of the main study sample?**

_____
(free text)

a) Not reported

-> Write numbers without separation marks, e.g.: 1503

Source: Custom-made

14. What was **the main study population?** *(refers to the study group of the main analysis, e.g., male > 65 yrs)*

_____
(free text)

a) General population
b) Not reported/ reference given
c) Not reported/ no reference given

Examples:	Healthy Adults, > 40 yrs	Men with CAD, 35 - 70 yrs, Nonsmoking

-> After each characteristic, separate by a comma and press ALT + Enter and use a new line

15. What was the sample type of the study population? Convenience/ Random sample?

a) Convenience sample
b) Random sample
c) Random + Convenience sample
d) Other
e) Not reported/ reference given
f) Not reported/ no reference given
g) Not applicable

-> No freetext answers allowed, if unclear state "Other".

-> random sample: Zufallsstichprobe au seiner vorhandenen Gesamtpopulation (es muss also eine Liste mit allen potentiellen Teilnehmern vorliegen). Z. B. Kohortenstudie, bei der aus dem Einwohnermelderegister zufällig gezogen wurde.

-> convenience: Probanden werden gezielt angesprochen, z. B. Bewohner in der Nähe eines Monitors, Kinder in Schulklassen, Kranke im Krankenhaus, etc. , convenience ist auch z. B. die ACS-study (Nachbarn und Freunde der ACS-Mitlgieder)

-> Mischform: z. B. aus allen Schulen einer Stadt werden 3 zufällig ausgewählt, dann werden die Kinder um Teilnahme gebeten. Oder Subgruppe einer größeren Kohorte (random sample), die bei einer Zusatzstudie mitmachen.

Source: Custom-made

16. **What was the response rate of the study**? [e.g., 58%] *If fewer than 50% of eligible persons participated in the study, then there is concern that the study population does not adequately represent the target population. This increases the risk of bias.*

_____

(free text)

a) Not reported/ reference given

b) Not reported/ no reference given

-> Time-series and convenience sample: not applicable.

Source: **Modified after question 3 of QAT** (Cohort and cross-sectional studies), with modified answer categories (see QAT in appendix).

17. Was a sample size justification or power description provided?

Did the authors present their reasons for selecting or recruiting the number of people included or analyzed? Do they note or discuss the statistical power of the study? This question is about whether or not the study had enough participants to detect an association if one truly existed. A paragraph in the methods section of the article may explain the sample size needed to detect a hypothesized difference in outcomes. You may also find a discussion of power in the discussion section (such as the study had 85 percent power to detect a 20 percent increase in the rate of an outcome of interest, with a 2-sided alpha of 0.05). Sometimes estimates of variance and/or estimates of effect size are given, instead of sample size calculations. In any of these cases, the answer would be "yes." However, ***observational cohort studies*** *often do not report anything about power or sample sizes because the analyses are exploratory in nature. In this case, the answer would be "no." This is not a "fatal flaw." It just may indicate that attention was not paid to whether the study was sufficiently sized to answer a prespecified question–i.e., it may have been an exploratory, hypothesis-generating study.*

a) Yes
b) Not reported/ reference given
c) Not reported/ no reference given
d) Not applicable

-> A simple reference to design paper is not sufficient. Select yes only in case that authors refer to a sample size calculation for this analysis.

Source: Modified after question 3 of QAT (Cohort and cross-sectional studies), with modified answer categories (see QAT in appendix).

18. Were all the subjects selected or recruited from the same or similar populations?

Were the same underlying criteria used for all of the subjects involved? This issue is related to the description of the study population, above, and you may find the information for both of these questions in the same section of the paper. Most ***cohort studies*** *begin with the selection of the cohort; participants in this cohort are then measured or evaluated to determine their exposure status. However, some cohort studies may recruit or select exposed participants in a different time or place than unexposed participants, especially retrospective cohort studies–which is when data are obtained from the past (retrospectively), but the analysis examines exposures prior to outcomes. For example, one research question could be whether diabetic men with clinical depression are at higher risk for cardiovascular disease*

than those without clinical depression. So, diabetic men with depression might be selected from a mental health clinic, while diabetic men without depression might be selected from an internal medicine or endocrinology clinic. This study recruits groups from different clinic populations, so this example would get a "no."

a) Yes
b) No
c) Not reported/ reference given
d) Not reported/ no reference given
e) Not applicable

Source: Modified after question 4 (part 1) of QAT (Cohort and cross-sectional studies), with modified answer categories (see QAT in appendix).

19. **If case-control study**, how was **the selection of controls**?
    a) Community controls
    b) Hospital controls
    c) Other
    d) Not reported/ reference given
    e) Not reported/ no reference given
    f) Not applicable

Source: Modified after **question 3 of NOS/**Selection (Case-control studies.

20. **If case-control study**, **were controls selected or recruited from the same or similar population that gave rise to the cases?** *To determine whether cases and controls were recruited from the same population, one can ask hypothetically, "If a control was to develop the outcome of interest (the condition that was used to select cases), would that person have been eligible to become a case?" Case-control studies begin with the selection of the cases (those with the outcome of interest, e.g., lung cancer) and controls (those in whom the outcome is absent). Cases and controls are then evaluated and categorized by their exposure status. For the lung cancer example, cases and controls were recruited from hospitals in a given region. One may reasonably assume that controls in the catchment area for the hospitals, or those already in the hospitals for a different reason, would attend those hospitals if they became a case; therefore, the controls are drawn from the same population as the cases. If the controls were recruited or selected from a different region (e.g., a State other than Texas) or time period (e.g., 1991-2000), then the cases and controls were recruited from different populations, and the answer to this question would be "no." The following **example** further explores selection of controls. In a study, eligible cases were men and women, ages 18 to 39, who were diagnosed with atherosclerosis at hospitals in Perth, Australia, between July 1, 2000 and December 31, 2007. Appropriate controls for these cases might be sampled using voter registration information for men and women ages 18 to 39, living in Perth (population-based controls); they also could be sampled from patients without atherosclerosis at the same hospitals (hospital-based controls). As long as the controls are individuals who would have been eligible to be included in the study as cases (if they had been diagnosed with atherosclerosis), then the controls were selected appropriately from the same source population as cases. In a prospective case-control study, investigators may enroll individuals as cases at the time they are found to have the outcome of interest; the number of cases usually increases as time progresses. At this same time, they may recruit or select controls from the population without the*

*outcome of interest. One way to identify or recruit cases is through a surveillance system. In turn, investigators can select controls from the population covered by that system. This is an example of population-based controls. Investigators also may identify and select cases from a **cohort study population** and identify controls from outcome-free individuals in the same cohort study. This is known as a nested case-control study.*

a) Yes
b) No
c) Not reported/ reference given
d) Not reported/no reference given
e) Not applicable

Source: Modified after **question 4 (part 1) of QAT** (Case-control studies).

21. **Were all the subjects selected or recruited from the same time period**? *(…) However, some cohort studies may recruit or select exposed participants in a different time or place than unexposed participants, especially retrospective cohort studies–which is when data are obtained from the past (retrospectively), but the analysis examines exposures prior to outcomes.*

a) Yes
b) No
c) Not reported/ reference given
d) Not reported/no reference given
e) Not applicable

Source: Modified after **question 4 (part 2) of QAT** (Cohort and cross-sectional studies)

22. **Were inclusion and exclusion criteria for being in the study prespecified?** *Were the inclusion and exclusion criteria developed prior to recruitment or selection of the study population?*

a) Yes
b) No
c) Not reported/ reference given
b) Not reported/no reference given
c) Not applicable

Source: Modified after **question 4 (part 3) of QAT** (Cohort and cross-sectional studies).

23. Is the analyzed sample representative for the general population?

a) Yes, completely representative.
b) Yes, somewhat representative.
b) Not representative/ selected group
d) Not applicable

Source: Modified after **question 1 of NOS/**Selection (Cohort studies).

- ➔ Completely representative only for whole population studies (time series, register-based, possibly also administrative data,
- ➔ For example if random sample of a subgroup, then b) for example a representative sample of all children or of all adults above a certain age

24. If cohort study: Is lost to follow-up after baseline provided?

a) Yes
b) Not reported/ reference given
c) Not reported/no reference given
d) Not applicable

25. **Are losses to follow-up likely to introduce bias?** *Higher overall follow-up rates are always better than lower follow-up rates, even though higher rates are expected in shorter studies, whereas lower overall follow-up rates are often seen in studies of longer duration. Usually, an acceptable overall follow-up rate is considered 80 percent or more of participants whose exposures were measured at baseline. However, this is just a general guideline. For example, a 6-month cohort study examining the relationship between dietary sodium intake and BP level may have over 90 percent follow-up, but a 20-year cohort study examining effects of sodium intake on stroke may have only a 65 percent follow-up rate.*

a) Yes
b) No
c) Cannot determine
d) Not applicable (e.g., if not reported)

Source: Modified after **question 13 of QAT** (Cohort and cross-sectional studies) and NOS/Outcome, Question 3 (Cohort studies)

26. What was the study period? [month/year]

(free text)

a) Not reported/ reference given
b) Not reported/no reference given
c) Not applicable

Example: ***03/2003-08/2004***

Source: Modified after HEI data extraction file (original: Study period, free text), answer categories inspired by QAT.

27. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed? *Did the study allow enough time for a sufficient number of outcomes to occur or be observed, or enough time for an exposure to have a biological effect on an outcome? In the examples given above, if clinical depression has a biological effect on increasing risk for CVD, such an effect may take years. In the other example, if higher dietary sodium increases BP, a short timeframe may be sufficient to assess its association with BP, but a longer timeframe would be needed to examine its association with heart attacks.*
The issue of timeframe is important to enable meaningful analysis of the relationships between exposures and outcomes to be conducted. This often requires at least several years, especially when looking at health outcomes, but it depends on the research question and outcomes being examined. ***Cross-sectional analyses*** *allow no time to see an effect, since the exposures and outcomes are assessed at the same time, so those would get a "no" response.*

a) Yes
b) No
a) Not reported/ reference given
b) Not reported/no reference given
c) Not applicable

Source: Modified after **question 7 of QAT** (Cohort and cross-sectional studies): Answer categories were modified.

27. **For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?** *This question is important because, in order to determine whether an exposure causes an outcome, the exposure must come before the outcome. For some prospective cohort studies, the investigator enrolls the cohort and then determines the exposure status of various members of the cohort (large epidemiological studies like Framingham used this approach). However, for other cohort studies, the cohort is selected based on its exposure status, as in the example above of depressed diabetic men (the exposure being depression). Other examples include a cohort identified by its exposure to fluoridated drinking water and then compared to a cohort living in an area without fluoridated water, or a cohort of military personnel exposed to combat in the Gulf War compared to a cohort of military personnel not deployed in a combat zone. With either of these types of cohort studies, the cohort is followed forward in time (i.e., prospectively) to assess the outcomes that occurred in the exposed members compared to nonexposed members of the cohort. Therefore, you begin the study in the present by looking at groups that were exposed (or not) to some biological or behavioral factor, intervention, etc., and then you follow them forward in time to examine outcomes. If a cohort study is conducted properly, the answer to this question should be "yes," since the exposure status of members of the cohort was determined at the beginning of the study before the outcomes occurred. For retrospective cohort studies, the same principal applies. The difference is that, rather than identifying a cohort in the present and following them forward in time, the investigators go back in time (i.e., retrospectively) and select a cohort based on their exposure status in the past and then follow them forward to assess the outcomes that occurred in the exposed and non-exposed cohort members. Because in retrospective cohort studies the exposure and outcomes may have already occurred (it depends on how long they follow the cohort), it is important to make sure that the exposure preceded the outcome. Sometimes cross-sectional studies are conducted (or cross-sectional analyses of cohort-study data), where the exposures and outcomes are measured during the same timeframe. As a result, cross-sectional analyses provide weaker evidence than regular cohort studies regarding a potential causal relationship between exposures and outcomes. For cross-sectional analyses, the answer to Question 6 should be "no."*

a) Yes

b) No

c) Not reported/ reference given

d) Not reported/ no reference given

d) Not applicable

Source: Modified after question 6 of QAT (Cohort and cross-sectional studies): Answer categories were modified.

c) Exposure assessment

28. Which type of exposure assessment technique was used (filter question)?

a) Model based

b) Measurements only

c) Other

-> No freetext answers allowed, if unclear state "Other".

Source: custom-made

29. If other exposure assessment technique was used, specify

(free text)

a) Not applicable

Source: custom-made

30. Which exposure assessment technique was used?

a) LUR

b) LUR: Spatio-temporal

c) CTM

d) Dispersion

e) Interpolation

f) Hybrid

g) Microscale personal exposure model

h) Measurement: satellite

i) Measurement: central site *(if only one measurement station was used)*

j) Measurement: residential

l) Measurement: mobile *(attached to car, bicycle, person)*

m) Other

-> No freetext answers allowed, if unclear state "Other".

Source: custom-made

31. If other exposure assessment technique was used, specify

(free text)

a) not applicable

32. What was the spatial resolution of the exposure? (E.g., 1x1km)

a) Mobile (for example personal or on bike or google cars)
b) Address-specific
c) Postal/ zip-code
d) City
e) 1x1 km^2
f) 5x5 km^2
g) 10x10 km^2
h) Other
i) No spatial resolution (for example only one monitor in one city)
j) Not reported/ reference given
k) Not reported/ no reference given

l) Not applicable

-> No freetext answers allowed, if unclear state "Other".

-> this only applies to the exposure assessment (model or measurements) and NOT to the assignment of exposure to the participants (separate question).

Source: custom-made

33. If other or unclear spatial resolution was used, specify

_____

(free text)

a) not applicable

34. **What was the temporal resolution of the exposure** measurement or modeling? Information on temp resol. of analysis in results section. Mehrfachnennung erlaubt [minute, hour, day, month, year, year-means].
If answer not included, specify as free text

_____

(free text)

a) Minute
b) Hour
c) Day
d) Month
e) Year
f) Year-means
g) Time-pattern
h) Not reported/ reference given

i) Not reported/ no reference given

j) Not applicable

Source: custom-made

35. To which level were the exposures allocated to participants?

If answer not included in list, specify as free text.

_____

(free text)

a) Mobile personal

b) Geocoded addresses (not corrected for mistakes in data base)

c) Microenvironments (incl. corrected addresses)

d) Zip code

e) City

f) County

g) Not reported/ reference given

h) Not reported/ no reference given

i) Not applicable

-> If exposure assessment was a central site measurement, select: "Not applicable"

Source: custom-made

36. Did the exposure assessment include a residential history?

a) Yes, complete or partial residential address history

b) No residential address history

c) Not reported / reference given

d) Not reported/ no reference given

e) Not applicable

*-> In case of **short-term studies**, select "not applicable"*

Source: custom-made

d) Assessment of UFP

37. Type of particle was assessed – UFP (ONLY below 100 nm) UFP in the most strict sense!

e) Yes

-> If UFP was not assessed, do not enter anything. The same procedure applies to the questions 39-42.

-> If the size fraction of UFP was not mentioned, select column 41) "Other" and specify as "not reported (42).

38. Type of particle was assessed – Quasi-UFP (PNC without cutpoint at 100 nm, for example total PNC or PNC 10-300 nm or PM0.25 or similar)

a) Yes

39. Type of particle was assessed – Surface Area

b) Yes

40. Type of particle was assessed - Other

c) Yes

41. If other type of particle was assessed, specify

_____
(free text)

b) Not reported

42. Particle metric - PNC?
-> If particle metric was not assessed, do not enter anything. The same pattern applies to the questions 44-51.

a) Yes

43. Particle metric – PM0.1?

b) Yes

44. Particle metric – PM0.25?

c) Yes

45. Particle metric – PM1.0?

d) Yes

46. Particle metric – Nucleation mode?

e) Yes

47. Particle metric – Aitken mode?

f) Yes

48. Particle metric – Accumulation mode?

g) Yes

49. Particle metric – Lung deposited surface area?

h) Yes

50. Particle metric – Other?

i) Yes

51. If other particle metric, specify

_____
(free text)

j) Not reported

52. Which size fractions were measured/modeled? Enter all fractions that were used in the analysis. Enter line change between each fraction (ALT + Enter)

x nm – y nm
(structured format)

a) Total
b) Not reported/ reference given
c) Not reported/ no reference given

d) Not applicable *(eg., LDSA)*

-> If no size fractions are mentioned, and a particle number counter was used, select "total"

Source: custom-made

53. **Which technical device was used to measure UFP?** (if various, give reference)

_____

(free text)

a) Various
b) Not reported/ reference given
c) Not reported/ no reference given
d) Not applicable

Source: custom-made

54. Was the measurement device/exposure model valid/reliable? (will be completed later)

55. Any mentioning of QA/QC measures described for the exposure assessment??

a) Yes
b) No
c) Not applicable

-> If a reference is given for QA/QC measures is given, select "Yes"

Source: custom-made

56. If QA/QC measures are referenced, specify

_____

(free text)

57. **Was the exposure assessment (independent variables) implemented consistently across all study participants?** Here is a final example that illustrates the point about why it is important to assess exposures consistently across all groups: If people with higher BP (exposed cohort) are seen by their providers more frequently than those without elevated BP (nonexposed group), it also increases the chances of detecting and documenting changes in health outcomes, including CVD-related events. Therefore, it may lead to the conclusion that higher BP leads to more CVD events. This may be true, but it could also be due to the fact that the subjects with higher BP were seen more often; thus, more CVD-related events were detected and documented simply because they had more encounters with the health care system. Thus, it could bias the results and lead to an erroneous conclusion.

a) Yes
b) No
c) Cannot determine
d) Not applicable

Source: Modified after **question 9** (partly) **of QAT**.

58. **Was the exposure assessment valid for the population?** Is the measurement/model appropriate to reflect the real exposure of the population?

a) Yes
b) No
c) Cannot determine
d) Not applicable

Source: Modified after **question 9 (partly) of QAT.**

59. **If cohort/panel/ crossover study, was the exposure assessed more than once over time?** Was the exposure for each person measured more than once during the course of the study period? Multiple measurements with the same result increase our confidence

that the exposure status was correctly classified. Also, multiple measurements enable investigators to look at changes in exposure over time, for example, people who ate high dietary sodium throughout the follow-up period, compared to those who started out high then reduced their intake, compared to those who ate low sodium throughout. Once again, this may not be applicable in all cases. In many older studies, exposure was measured only at baseline. However, multiple exposure measurements do result in a stronger study design.

a) Yes
b) No
c) Not reported/ reference given
d) Not reported/ no reference given
e) Not applicable

Source: Modified after QAT, Question 10 (answer categories).

f) Assessment of other exposures (air pollutants, noise, meteorologic data)

60. Were other air pollutants assessed?

f) Yes
g) No
h) Not applicable

Source: custom-made

Which technical device/exposure model was used to assess other air pollutants?

_____
(free text)

a) Not reported/ reference given

b) Not reported/ no reference given

c) Not applicable

-> If various, give reference

Source: custom-made

61. Was noise exposure assessed?

a) Yes, on residential level

b) Yes, on personal level

c) Yes, other

d) No

Source: custom-made

62. Was meteorological data measured/ modeled? (filter question)

a) Yes

b) No

c) Not applicable

Source: custom-made

63. Which meteorological data measured/ modeled? (MN)

If answer not included in list, specify as free text.

a) Temperature

b) Relative humidity

c) Barometric pressure

d) Precipitation

e) Season

f) Pollen counts
g) Other
h) Wind speed and direction
i) Not reported/ reference given
j) Not reported/ no reference given
k) Not applicable

Source: custom-made

64. How was meteorological data measured/ modeled? (MN)

a) Routine measurement
b) Study-specific measurement
c) Other
d) Not reported/ reference given
e) Not reported/ no reference given
f) Not applicable

Source: custom-made

65. Was neighborhood SES assessed? (filter question)

a) Yes
b) Not reported/ reference given
c) Not reported/ no reference given
d) Not applicable

Source: custom-made

66. How was neighborhood SES data measured/ modeled?

_____

(free text)

l) Not reported/ reference given
m) Not reported/ no reference given
n) Not applicable

Source: custom-made

67. What was the average submicron particle exposure of the study population (main analysis)?

_____
(free text)

a) Not reported/ reference given
b) Not reported/ no reference given
c) Not applicable

-> Specify if Mean or Median and add SD/IQR, if given.

-> Write numbers **without** any separation marks (“,” or “.”)

Example: Mean (SD): 15000 (4000)

Median (IQR): 13500 (3500)

g) Outcome assessment

68. Which outcome type was assessed? - Mortality

a) Yes

69. **Which outcome type was assessed? - Morbidity** (except emergency/admissions, etc.)

b) Yes

-> Code symptoms as morbidity

-> Except emergency/ hospital visits/admissions – see next question

70. Which outcome type was assessed? - Emergency/ hospital/ visits/ admissions

c) Yes

71. Which outcome type was assessed? - Subclinical

d) Yes

72. Which outcome type was assessed? - Other

e) Yes

Source: Custom-made

73. What was the main outcome of the study?

a) Total Mortality
b) Cardiovascular
c) Respiratory and atopy
d) inflammation
e) Oxidative stress
f) Neurocognitive
g) Other

-> No freetext answers allowed, if unclear state "Other".

74. What was/were the specific outcome(s) of the study

_____
(free text)

d) Not reported/ reference given
e) Not reported/ no reference given
f) Not applicable

Source: custom-made

75. Were the outcome measures (dependent variables) clearly defined and implemented consistently across all study participants?

a) Yes
b) No
c) Not applicable

Source: Modified after **question 11 (partly) of QAT**.

76. How was the outcome assessed?

a) Standardized clinical examinations (e.g., in study center)
b) Official registry *(e.g., cancer registry)*
c) Administrative database *(e.g., insurance companies)*
d) Medical records *(e.g., hospital, general practitioner)*
e) Self-reported physician-diagnosed
f) Self-reported
g) Mobile device
h) Other

Source: custom-made

77. What was/were the ICD-codes of the outcome(s)?

_____

(free text)

a) Not reported
b) Not applicable

Source: custom-made

h) Statistical analysis

78. Which type of analysis was used?

a) Group comparison
b) Linear regression
c) Mixed linear regression
d) Logistic regression
e) Poisson regression
f) Cox-regression
g) Additive mixed model
h) Generalized estimated equation (GEE)
i) Other
j) Not reported/ reference given
k) Not reported/ no reference given
l) Not applicable

Source: custom-made

79. Which effect measure was estimated?

a) ß-estimates
b) %-change
c) OR
d) RR
e) HR
f) Other
g) No quantitative effect measures
h) Not applicable

Source: custom-made

80. Which unit of exposure was used?

a) Group comparison *(<=2)*
b) Categories *(>2)*
c) Fixed increment
d) IQR
e) Distribution based
f) Other
g) Not applicable

Source: custom-made

81.Absolute size of exposure unit?

_____
(free text)

c) Not reported

d) Not applicable

-> Write numbers without separation marks

Source: custom-made

82. Were the outcome assessors blinded to the exposure status resp. Case-control status of participants? Blinding means that outcome assessors did not know whether the participant was exposed or unexposed. It is also sometimes called "masking." The objective is to look for evidence in the article that the person(s) assessing the outcome(s) for the study (for example, examining medical records to determine the outcomes that occurred in the exposed and comparison groups) is masked to the exposure status of the participant. Sometimes the person measuring the exposure is the same person conducting the outcome assessment. In this case, the outcome assessor would most likely not be blinded to exposure status because they also took measurements of exposures. If so, make a note of that in the comments section.

a) Yes
b) No
c) Not reported/ reference given
d) Not reported/ no reference given
e) Not applicable

Source: Question 12 of QAT (Cohort and Cross-sectional, modified in question 11 (Case-Control))

83. Was the analysis adjusted for personal covariates? (e.g. demographic, lifestyle, medication)

a) Extensively
b) For main covariates
c) For some covariates
d) No
e) Not reported/ reference given
f) Not reported/ no reference given
g) Not applicable

Source: custom-made

84. Was the analysis adjusted for socioeconomic covariates?

a) Yes
b) No
c) Not reported/ reference given
d) Not reported/ no reference given
e) Not applicable

Source: custom-made

85. **Was the analysis adjusted for environmental covariates - NOISE?**

a) Yes

86. **Was the analysis adjusted for environmental covariates - METEOROLOGY**?

b) Yes

87. **Was the analysis adjusted for environmental covariates – Neighborhood SES?**

c) Yes

88. **Was the analysis adjusted for environmental covariates - Other?**

a) Yes

89. If adjusted for other environmental covariates, specify.

_____
(free text)

e) Not reported

f) Not applicable

Source: custom-made

90. Was the analysis adjusted for other air pollutants? / Were multi-pollutant-models conducted?

a) Yes
b) No
c) Not reported/ reference given
d) Not reported/ no reference given
e) Not applicable

Source: custom-made

91. For which co-pollutants were UFP-models adjusted?

_____
(free text)

g) Not reported

92. Covariate adjustment: List/ Specify

_____
(free text)

h) Not reported

-> Separate by commas, use capital letter for first entry, e.g.:

-> Age, dyslipidemia, prior MI, smoking, year, weekday, hour of the day, temperature, relative humidity

-> In case of different adjustment sets, separate by a), b), c) etc.

Source: custom-made

93. **Was confounder adjustment adequate?** Were key potential confounding variables measured and adjusted for, such as by statistical adjustment for baseline differences? Logistic regression or other regression methods are often used to account for the influence of variables not of interest. This is a key issue in cohort studies, because statistical analyses need to control for potential confounders, in contrast to an RCT, where the randomization process controls for potential confounders. All key factors that may be associated both with the exposure of interest and the outcome–that are not of interest to the research question–should be controlled for in the analyses. For example, in a study of the relationship between cardiorespiratory fitness and CVD events (heart attacks and strokes), the study should control for age, BP, blood cholesterol, and body weight, because all of these factors are associated both with low fitness and with CVD events. Well-done cohort studies control for multiple potential confounders.

a) Yes
b) Partly
c) No
d) Not applicable

Source: Modified after **question 14 of QAT** (Cohort and cross-sectional).

94. **If case-control and matching was used, did the investigators account for matching during study analysis?** Matching is a technique used to improve study efficiency and control for known confounders. For example, in the study of smoking and CVD events, an investigator might identify cases that have had a heart attack or stroke and then select controls of similar age, gender, and body weight to the cases. For case-control studies, it is important that if matching was performed during the selection or recruitment process, the variables used as matching criteria (e.g., age, gender, race) should be controlled for in the analysis.

a) Yes
b) No
c) Not reported/ reference given
d) Not reported/ no reference given
e) Not applicable

Source: Modified after **question 12 (part 2) of QAT** (Case-control studies)

95. For UFP-effect w/o co-pollutant adjustment: Was at least 1 estimate significantly elevated in the eypected adverse direction?

a) Yes

b) No

c) Not applicable

Source: custom-made

➔ If not clear, wich direction is expected and "adverse", generalize here to significantly changed

96. For UFP-effects w/o co-pollutant adjustment: Was a general pattern consistent with adverse association, regardless of significance?

a) Yes

b) No

c) Not applicable

Source: custom-made

97. For UFP-effect w/o co-pollutant adjustment: Were significant protective associations observed?

a) Yes

b) No

c) Not applicable

Source: custom-made

98. For UFP-effect with co-pollutant adjustment: Was at least 1 estimate significantly elevated in the expected adverse direction?

a) Yes

b) No

c) Not applicable

Source: custom-made

➔ If not clear, wich direction is expected and "adverse", generalize here to significantly changed

99. For UFP-effects with co-pollutant adjustment: Was a general pattern consistent with adverse association, regardless of significance?

a) Yes

b) No

c) Not applicable

Source: custom-made

100. For UFP-effect w/o co-pollutant adjustment: Were significant protective associations observed?

a) Yes

b) No

c) Not applicable

Source: custom-made

101. What was/were the size (incl. confidence intervals) of the UFP effect(s)? give estimate with most complete adjustment set. If estimate with and without copollutant is given, report both.

_____

(free text)

a) Not applicable

-> Use one line per estimate, write confidence intervals, separated by "-" in round brackets behind estimate).

-> In case of different outcomes/time lags, specify outcome/lag before estimates.

E.g.: 1-day: 1.03 (1.00-1.03)

2-day: 1.05 (1.02-1.07)

Source: custom-made

102. Was the model robust to the adjustment of other pollutant effects?

a) Yes
b) Mainly
c) Partly
d) No
e) Not applicable *(e.g., no adjustment for other pollutants)*

Source: custom-made

103. What was/were the effect size(s) of other pollutants?

_____
(free text)

a) Not reported/ reference given
b) Not reported/ no reference given
c) Not applicable

-> Format as UFP effect sizes.

-> Reference to table possible

Source: custom-made

104. Was the effect of other pollutants robust upon the inclusion of UFP?

a) Yes
b) Mainly
c) Partly
d) No
e) Not applicable *(e.g., no adjustment for UFP)*

Source: custom-made

105. Do sensitivity analyses support robustness of the associations? Does the main conclusion stays the same?

a) Yes

b) Partly

c) No

d) Not applicable *(e.g., no sensitivity analyses)*

Source: custom-made

106. Comments

_____

(free text)

107. Ersteingabe:

-> Name

108. Zweiteingabe

-> Name

109. Datum der Eingabe

-> z.B. 15.10.2017

Annexes

Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the research question or objective in this paper clearly stated?			
2. Was the study population clearly specified and defined?			
3. Was the participation rate of eligible persons at least 50%?			
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?			
5. Was a sample size justification, power description, or variance and effect estimates provided?			
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?			
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?			
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?			
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			
10. Was the exposure(s) assessed more than once over time?			
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			
12. Were the outcome assessors blinded to the exposure status of participants?			
13. Was loss to follow-up after baseline 20% or less?			
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?			

Quality Rating (Good, Fair, or Poor) (see guidance)

Rater #1 initials:

Rater #2 initials:

Additional Comments (If POOR, please state why):

*CD, cannot determine; NA, not applicable; NR, not reported

Guidance for Assessing the Quality of Observational Cohort and Cross-Sectional Studies

The guidance document below is organized by question number from the tool for quality assessment of observational cohort and cross-sectional studies.

Question 1. Research question

Did the authors describe their goal in conducting this research? Is it easy to understand what they were looking to find? This issue is important for any scientific paper of any type. Higher quality scientific research explicitly defines a research question.

Questions 2 and 3. Study population

Did the authors describe the group of people from which the study participants were selected or recruited, using demographics, location, and time period? If you were to conduct this study again, would you know who to recruit, from where, and from what time period? Is the cohort population free of the outcomes of interest at the time they were recruited?

An example would be men over 40 years old with type 2 diabetes who began seeking medical care at Phoenix Good Samaritan Hospital between January 1, 1990 and December 31, 1994.

In this example, the population is clearly described as: (1) who (men over 40 years old with type 2 diabetes); (2) where (Phoenix Good Samaritan Hospital); and (3) when (between January 1, 1990 and December 31, 1994). Another example is women ages 34 to 59 years of age in 1980 who were in the nursing profession and had no known coronary disease, stroke, cancer, hypercholesterolemia, or diabetes, and were recruited from the 11 most populous States, with contact information obtained from State nursing boards.

In cohort studies, it is crucial that the population at baseline is free of the outcome of interest. For example, the nurses' population above would be an appropriate group in which to study incident coronary disease. This information is usually found either in descriptions of population recruitment, definitions of variables, or inclusion/exclusion criteria.

You may need to look at prior papers on methods in order to make the assessment for this question. Those papers are usually in the reference list.

If fewer than 50% of eligible persons participated in the study, then there is concern that the study population does not adequately represent the target population. This increases the risk of bias.

Question 4. Groups recruited from the same population and uniform eligibility criteria

Were the inclusion and exclusion criteria developed prior to recruitment or selection of the study population? Were the same underlying criteria used for all of the subjects involved? This issue is related to the description of the study population, above, and you may find the information for both of these questions in the same section of the paper.

Most cohort studies begin with the selection of the cohort; participants in this cohort are then measured or evaluated to determine their exposure status. However, some cohort studies may recruit or select exposed participants in a different time or place than unexposed participants, especially retrospective cohort studies–which is when data are obtained from

the past (retrospectively), but the analysis examines exposures prior to outcomes. For example, one research question could be whether diabetic men with clinical depression are at higher risk for cardiovascular disease than those without clinical depression. So, diabetic men with depression might be selected from a mental health clinic, while diabetic men without depression might be selected from an internal medicine or endocrinology clinic. This study recruits groups from different clinic populations, so this example would get a "no."

However, the women nurses described in the question above were selected based on the same inclusion/exclusion criteria, so that example would get a "yes."

Question 5. Sample size justification

Did the authors present their reasons for selecting or recruiting the number of people included or analyzed? Do they note or discuss the statistical power of the study? This question is about whether or not the study had enough participants to detect an association if one truly existed.

A paragraph in the methods section of the article may explain the sample size needed to detect a hypothesized difference in outcomes. You may also find a discussion of power in the discussion section (such as the study had 85 percent power to detect a 20 percent increase in the rate of an outcome of interest, with a 2-sided alpha of 0.05). Sometimes estimates of variance and/or estimates of effect size are given, instead of sample size calculations. In any of these cases, the answer would be "yes."

However, observational cohort studies often do not report anything about power or sample sizes because the analyses are exploratory in nature. In this case, the answer would be "no." This is not a "fatal flaw." It just may indicate that attention was not paid to whether the study was sufficiently sized to answer a prespecified question–i.e., it may have been an exploratory, hypothesis-generating study.

Question 6. Exposure assessed prior to outcome measurement

This question is important because, in order to determine whether an exposure causes an outcome, the exposure must come before the outcome.

For some prospective cohort studies, the investigator enrolls the cohort and then determines the exposure status of various members of the cohort (large epidemiological studies like Framingham used this approach). However, for other cohort studies, the cohort is selected based on its exposure status, as in the example above of depressed diabetic men (the exposure being depression). Other examples include a cohort identified by its exposure to fluoridated drinking water and then compared to a cohort living in an area without fluoridated water, or a cohort of military personnel exposed to combat in the Gulf War compared to a cohort of military personnel not deployed in a combat zone.

With either of these types of cohort studies, the cohort is followed forward in time (i.e., prospectively) to assess the outcomes that occurred in the exposed members compared to nonexposed members of the cohort. Therefore, you begin the study in the present by looking at groups that were exposed (or not) to some biological or behavioral factor, intervention, etc., and then you follow them forward in time to examine outcomes. If a cohort study is conducted properly, the answer to this question should be "yes," since the exposure status of members of the cohort was determined at the beginning of the study before the outcomes occurred.

For retrospective cohort studies, the same principal applies. The difference is that, rather than identifying a cohort in the present and following them forward in time, the investigators go back in time (i.e., retrospectively) and select a cohort based on their exposure status in the past and then follow them forward to assess the outcomes that occurred in the exposed and nonexposed cohort members. Because in retrospective cohort studies the exposure and outcomes may have already occurred (it depends on how long they follow the cohort), it is important to make sure that the exposure preceded the outcome.

Sometimes cross-sectional studies are conducted (or cross-sectional analyses of cohort-study data), where the exposures and outcomes are measured during the same timeframe.

As a result, cross-sectional analyses provide weaker evidence than regular cohort studies regarding a potential causal relationship between exposures and outcomes. For cross-sectional analyses, the answer to Question 6 should be "no."

Question 7. Sufficient timeframe to see an effect

Did the study allow enough time for a sufficient number of outcomes to occur or be observed, or enough time for an exposure to have a biological effect on an outcome? In the examples given above, if clinical depression has a biological effect on increasing risk for CVD, such an effect may take years. In the other example, if higher dietary sodium increases BP, a short timeframe may be sufficient to assess its association with BP, but a longer timeframe would be needed to examine its association with heart attacks.

The issue of timeframe is important to enable meaningful analysis of the relationships between exposures and outcomes to be conducted. This often requires at least several years, especially when looking at health outcomes, but it depends on the research question and outcomes being examined.

Cross-sectional analyses allow no time to see an effect, since the exposures and outcomes are assessed at the same time, so those would get a "no" response.

Question 8. Different levels of the exposure of interest

If the exposure can be defined as a range (examples: drug dosage, amount of physical activity, amount of sodium consumed), were multiple categories of that exposure assessed? (for example, for drugs: not on the medication, on a low dose, medium dose, high dose; for dietary sodium, higher than average U.S. consumption, lower than recommended consumption, between the two). Sometimes discrete categories of exposure are not used, but instead exposures are measured as continuous variables (for example, mg/day of dietary sodium or BP values).

In any case, studying different levels of exposure (where possible) enables investigators to assess trends or dose-response relationships between exposures and outcomes–e.g., the higher the exposure, the greater the rate of the health outcome. The presence of trends or dose-response relationships lends credibility to the hypothesis of causality between exposure and outcome.

For some exposures, however, this question may not be applicable (e.g., the exposure may be a dichotomous variable like living in a rural setting versus an urban setting, or vaccinated/not vaccinated with a one-time vaccine). If there are only two possible exposures (yes/no), then this question should be given an "NA," and it should not count negatively towards the quality rating.

Question 9. Exposure measures and assessment

Were the exposure measures defined in detail? Were the tools or methods used to measure exposure accurate and reliable–for example, have they been validated or are they objective? This issue is important as it influences confidence in the reported exposures. When exposures are measured with less accuracy or validity, it is harder to see an association between exposure and outcome even if one exists. Also as important is whether the exposures were assessed in the same manner within groups and between groups; if not, bias may result.

For example, retrospective self-report of dietary salt intake is not as valid and reliable as prospectively using a standardized dietary log plus testing participants' urine for sodium content. Another example is measurement of BP, where there may be quite a difference between usual care, where clinicians measure BP however it is done in their practice setting (which can vary considerably), and use of trained BP assessors using standardized equipment (e.g., the same BP device which has been tested and calibrated) and a standardized protocol (e.g., patient is seated for 5 minutes with feet flat on the floor, BP is taken twice in each arm, and all four measurements are averaged). In each of these cases, the former would get a "no" and the latter a "yes."

Here is a final example that illustrates the point about why it is important to assess exposures consistently across all groups: If people with higher BP (exposed cohort) are seen by their providers more frequently than those without elevated BP (nonexposed group), it also increases the chances of detecting and documenting changes in health outcomes, including CVD-related events. Therefore, it may lead to the conclusion that higher BP leads to more CVD events. This may be true, but it could also be due to the fact that the subjects with higher BP were seen more often; thus, more CVD-related events were detected and documented simply because they had more encounters with the health care system. Thus, it could bias the results and lead to an erroneous conclusion.

Question 10. Repeated exposure assessment

Was the exposure for each person measured more than once during the course of the study period? Multiple measurements with the same result increase our confidence that the exposure status was correctly classified. Also, multiple measurements enable investigators to look at changes in exposure over time, for example, people who ate high dietary sodium throughout the followup period, compared to those who started out high then reduced their intake, compared to those who ate low sodium throughout. Once again, this may not be applicable in all cases. In many older studies, exposure was measured only at baseline. However, multiple exposure measurements do result in a stronger study design.

Question 11. Outcome measures

Were the outcomes defined in detail? Were the tools or methods for measuring outcomes accurate and reliable–for example, have they been validated or are they objective? This issue is important because it influences confidence in the validity of study results. Also important is whether the outcomes were assessed in the same manner within groups and between groups.

An example of an outcome measure that is objective, accurate, and reliable is death–the outcome measured with more accuracy than any other. But even with a measure as objective as death, there can be differences in the accuracy and reliability of how death was assessed by

the investigators. Did they base it on an autopsy report, death certificate, death registry, or report from a family member? Another example is a study of whether dietary fat intake is related to blood cholesterol level (cholesterol level being the outcome), and the cholesterol level is measured from fasting blood samples that are all sent to the same laboratory. These examples would get a "yes." An example of a "no" would be self-report by subjects that they had a heart attack, or self-report of how much they weigh (if body weight is the outcome of interest).

Similar to the example in Question 9, results may be biased if one group (e.g., people with high BP) is seen more frequently than another group (people with normal BP) because more frequent encounters with the health care system increases the chances of outcomes being detected and documented.

Question 12. Blinding of outcome assessors

Blinding means that outcome assessors did not know whether the participant was exposed or unexposed. It is also sometimes called "masking." The objective is to look for evidence in the article that the person(s) assessing the outcome(s) for the study (for example, examining medical records to determine the outcomes that occurred in the exposed and comparison groups) is masked to the exposure status of the participant. Sometimes the person measuring the exposure is the same person conducting the outcome assessment. In this case, the outcome assessor would most likely not be blinded to exposure status because they also took measurements of exposures. If so, make a note of that in the comments section.

As you assess this criterion, think about whether it is likely that the person(s) doing the outcome assessment would know (or be able to figure out) the exposure status of the study participants. If the answer is no, then blinding is adequate. An example of adequate blinding of the outcome assessors is to create a separate committee, whose members were not involved in the care of the patient and had no information about the study participants' exposure status. The committee would then be provided with copies of participants' medical records, which had been stripped of any potential exposure information or personally identifiable information. The committee would then review the records for prespecified outcomes

according to the study protocol. If blinding was not possible, which is sometimes the case, mark "NA" and explain the potential for bias.

Question 13. Followup rate

Higher overall followup rates are always better than lower followup rates, even though higher rates are expected in shorter studies, whereas lower overall followup rates are often seen in studies of longer duration. Usually, an acceptable overall followup rate is considered 80 percent or more of participants whose exposures were measured at baseline. However, this is just a general guideline. For example, a 6-month cohort study examining the relationship between dietary sodium intake and BP level may have over 90 percent followup, but a 20-year cohort study examining effects of sodium intake on stroke may have only a 65 percent followup rate.

Question 14. Statistical analyses

Were key potential confounding variables measured and adjusted for, such as by statistical adjustment for baseline differences? Logistic regression or other regression methods are often used to account for the influence of variables not of interest.

This is a key issue in cohort studies, because statistical analyses need to control for potential confounders, in contrast to an RCT, where the randomization process controls for potential confounders. All key factors that may be associated both with the exposure of interest and the outcome–that are not of interest to the research question–should be controlled for in the analyses.

For example, in a study of the relationship between cardiorespiratory fitness and CVD events (heart attacks and strokes), the study should control for age, BP, blood cholesterol, and body weight, because all of these factors are associated both with low fitness and with CVD events. Well-done cohort studies control for multiple potential confounders.

Some general guidance for determining the overall quality rating of observational cohort and cross-sectional studies

The questions on the form are designed to help you focus on the key concepts for evaluating the internal validity of a study. They are not intended to create a list that you simply tally up to arrive at a summary judgment of quality.

Internal validity for cohort studies is the extent to which the results reported in the study can truly be attributed to the exposure being evaluated and not to flaws in the design or conduct of the study–in other words, the ability of the study to draw associative conclusions about the effects of the exposures being studied on outcomes. Any such flaws can increase the risk of bias.

Critical appraisal involves considering the risk of potential for selection bias, information bias, measurement bias, or confounding (the mixture of exposures that one cannot tease out from each other). Examples of confounding include co-interventions, differences at baseline in patient characteristics, and other issues throughout the questions above. High risk of bias translates to a rating of poor quality. Low risk of bias translates to a rating of good quality. (Thus, the greater the risk of bias, the lower the quality rating of the study.)

In addition, the more attention in the study design to issues that can help determine whether there is a causal relationship between the exposure and outcome, the higher quality the study. These include exposures occurring prior to outcomes, evaluation of a dose-response gradient, accuracy of measurement of both exposure and outcome, sufficient timeframe to see an effect, and appropriate control for confounding–all concepts reflected in the tool.

Generally, when you evaluate a study, you will not see a "fatal flaw," but you will find some risk of bias. By focusing on the concepts underlying the questions in the quality assessment tool, you should ask yourself about the potential for bias in the study you are critically appraising. For any box where you check "no" you should ask, "What is the potential risk of bias resulting from this flaw in study design or execution?" That is, does this factor cause you to

doubt the results that are reported in the study or doubt the ability of the study to accurately assess an association between exposure and outcome?

The best approach is to think about the questions in the tool and how each one tells you something about the potential for bias in a study. The more you familiarize yourself with the key concepts, the more comfortable you will be with critical appraisal. Examples of studies rated good, fair, and poor are useful, but each study must be assessed on its own based on the details that are reported and consideration of the concepts for minimizing bias.

Last Updated March 2014

Quality Assessment of Case-Control Studies

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the research question or objective in this paper clearly stated and appropriate?			
2. Was the study population clearly specified and defined?			
3. Did the authors include a sample size justification?			
4. Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?			
5. Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?			
6. Were the cases clearly defined and differentiated from controls?			
7. If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?			
8. Was there use of concurrent controls?			
9. Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?			
10. Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (includingthe same time period) across all study participants?			
11. Were the assessors of exposure/risk blinded to the case or control status of participants?			
12. Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?			
Quality Rating (Good, Fair, or Poor) (see guidance)			
Rater #1 initials:			
Rater #2 initials:			
Additional Comments (If POOR, please state why):			

*CD, cannot determine; NA, not applicable; NR, not reported

Guidance for Assessing the Quality of Case-Control Studies

The guidance document below is organized by question number from the tool for quality assessment of case-control studies.

Question 1. Research question

Did the authors describe their goal in conducting this research? Is it easy to understand what they were looking to find? This issue is important for any scientific paper of any type. High quality scientific research explicitly defines a research question.

Question 2. Study population

Did the authors describe the group of individuals from which the cases and controls were selected or recruited, while using demographics, location, and time period? If the investigators conducted this study again, would they know exactly who to recruit, from where, and from what time period?

Investigators identify case-control study populations by location, time period, and inclusion criteria for cases (individuals with the disease, condition, or problem) and controls (individuals without the disease, condition, or problem). For example, the population for a study of lung cancer and chemical exposure would be all incident cases of lung cancer diagnosed in patients ages 35 to 79, from January 1, 2003 to December 31, 2008, living in Texas during that entire time period, as well as controls without lung cancer recruited from the same population during the same time period. The population is clearly described as: (1) who (men and women ages 35 to 79 with (cases) and without (controls) incident lung cancer); (2) where (living in Texas); and (3) when (between January 1, 2003 and December 31, 2008).

Other studies may use disease registries or data from cohort studies to identify cases. In these cases, the populations are individuals who live in the area covered by the disease registry or included in a cohort study (i.e., nested case-control or case-cohort). For example, a study of the relationship between vitamin D intake and myocardial infarction might use patients identified via the GRACE registry, a database of heart attack patients.

NHLBI staff encouraged reviewers to examine prior papers on methods (listed in the reference list) to make this assessment, if necessary.

Question 3. Target population and case representation

In order for a study to truly address the research question, the target population–the population from which the study population is drawn and to which study results are believed to apply–should be carefully defined. Some authors may compare characteristics of the study cases to characteristics of cases in the target population, either in text or in a table. When

study cases are shown to be representative of cases in the appropriate target population, it increases the likelihood that the study was well-designed per the research question.

However, because these statistics are frequently difficult or impossible to measure, publications should not be penalized if case representation is not shown. For most papers, the response to question 3 will be "NR." Those subquestions are combined because the answer to the second subquestion–case representation–determines the response to this item. However, it cannot be determined without considering the response to the first subquestion. For example, if the answer to the first subquestion is "yes," and the second, "CD," then the response for item 3 is "CD."

Question 4. Sample size justification

Did the authors discuss their reasons for selecting or recruiting the number of individuals included? Did they discuss the statistical power of the study and provide a sample size calculation to ensure that the study is adequately powered to detect an association (if one exists)? This question does not refer to a description of the manner in which different groups were included or excluded using the inclusion/exclusion criteria (e.g., "Final study size was 1,378 participants after exclusion of 461 patients with missing data" is not considered a sample size justification for the purposes of this question).

An article's methods section usually contains information on sample size and the size needed to detect differences in exposures and on statistical power.

Question 5. Groups recruited from the same population

To determine whether cases and controls were recruited from the same population, one can ask hypothetically, "If a control was to develop the outcome of interest (the condition that was used to select cases), would that person have been eligible to become a case?" Case-control studies begin with the selection of the cases (those with the outcome of interest, e.g., lung cancer) and controls (those in whom the outcome is absent). Cases and controls are then evaluated and categorized by their exposure status. For the lung cancer example, cases and controls were recruited from hospitals in a given region. One may reasonably assume that controls in the catchment area for the hospitals, or those already in the hospitals for a different reason, would attend those hospitals if they became a case; therefore, the controls are drawn from the same population as the cases. If the controls were recruited or selected from a different region (e.g., a State other than Texas) or time period (e.g., 1991-2000), then the cases and controls were recruited from different populations, and the answer to this question would be "no."

The following example further explores selection of controls. In a study, eligible cases were men and women, ages 18 to 39, who were diagnosed with atherosclerosis at hospitals in Perth, Australia, between July 1, 2000 and December 31, 2007. Appropriate controls for these cases might be sampled using voter registration information for men and women ages 18 to 39, living in Perth (population-based controls); they also could be sampled from patients without atherosclerosis at the same hospitals (hospital-based controls). As long as the controls are individuals who would have been eligible to be included in the study as cases (if they had been diagnosed with atherosclerosis), then the controls were selected appropriately from the same source population as cases.

In a prospective case-control study, investigators may enroll individuals as cases at the time they are found to have the outcome of interest; the number of cases usually increases as time progresses. At this same time, they may recruit or select controls from the population without the outcome of interest. One way to identify or recruit cases is through a surveillance system. In turn, investigators can select controls from the population covered by that system. This is an example of population-based controls. Investigators also may identify and select cases from a cohort study population and identify controls from outcome-free individuals in the same cohort study. This is known as a nested case-control study.

Question 6. Inclusion and exclusion criteria prespecified and applied uniformly

Were the inclusion and exclusion criteria developed prior to recruitment or selection of the study population? Were the same underlying criteria used for all of the groups involved? To answer this question, reviewers determined if the investigators developed I/E criteria prior to recruitment or selection of the study population and if they used the same underlying criteria for all groups. The investigators should have used the same selection criteria, except for study participants who had the disease or condition, which would be different for cases and controls by definition. Therefore, the investigators use the same age (or age range), gender, race, and other characteristics to select cases and controls. Information on this topic is usually found in a paper's section on the description of the study population.

Question 7. Case and control definitions

For this question, reviewers looked for descriptions of the validity of case and control definitions and processes or tools used to identify study participants as such. Was a specific description of "case" and "control" provided? Is there a discussion of the validity of the case and control definitions and the processes or tools used to identify study participants as such? They determined if the tools or methods were accurate, reliable, and objective. For example, cases might be identified as "adult patients admitted to a VA hospital from January 1, 2000

to December 31, 2009, with an ICD-9 discharge diagnosis code of acute myocardial infarction and at least one of the two confirmatory findings in their medical records: at least 2mm of ST elevation changes in two or more ECG leads and an elevated troponin level. Investigators might also use ICD-9 or CPT codes to identify patients. All cases should be identified using the same methods. Unless the distinction between cases and controls is accurate and reliable, investigators cannot use study results to draw valid conclusions.

Question 8. Random selection of study participants

If a case-control study did not use 100 percent of eligible cases and/or controls (e.g., not all disease-free participants were included as controls), did the authors indicate that random sampling was used to select controls? When it is possible to identify the source population fairly explicitly (e.g., in a nested case-control study, or in a registry-based study), then random sampling of controls is preferred. When investigators used consecutive sampling, which is frequently done for cases in prospective studies, then study participants are not considered randomly selected. In this case, the reviewers would answer "no" to Question 8. However, this would not be considered a fatal flaw.

If investigators included all eligible cases and controls as study participants, then reviewers marked "NA" in the tool. If 100 percent of cases were included (e.g., NA for cases) but only 50 percent of eligible controls, then the response would be "yes" if the controls were randomly selected, and "no" if they were not. If this cannot be determined, the appropriate response is "CD."

Question 9. Concurrent controls

A concurrent control is a control selected at the time another person became a case, usually on the same day. This means that one or more controls are recruited or selected from the population without the outcome of interest at the time a case is diagnosed. Investigators can use this method in both prospective case-control studies and retrospective case-control studies. For example, in a retrospective study of adenocarcinoma of the colon using data from hospital records, if hospital records indicate that Person A was diagnosed with adenocarcinoma of the colon on June 22, 2002, then investigators would select one or more controls from the population of patients without adenocarcinoma of the colon on that same day. This assumes they conducted the study retrospectively, using data from hospital records. The investigators could have also conducted this study using patient records from a cohort study, in which case it would be a nested case-control study.

Investigators can use concurrent controls in the presence or absence of matching and vice versa. A study that uses matching does not necessarily mean that concurrent controls were used.

Question 10. Exposure assessed prior to outcome measurement

Investigators first determine case or control status (based on presence or absence of outcome of interest), and then assess exposure history of the case or control; therefore, reviewers ascertained that the exposure preceded the outcome. For example, if the investigators used tissue samples to determine exposure, did they collect them from patients prior to their diagnosis? If hospital records were used, did investigators verify that the date a patient was exposed (e.g., received medication for atherosclerosis) occurred prior to the date they became a case (e.g., was diagnosed with type 2 diabetes)? For an association between an exposure and an outcome to be considered causal, the exposure must have occurred prior to the outcome.

Question 11. Exposure measures and assessment

Were the exposure measures defined in detail? Were the tools or methods used to measure exposure accurate and reliable–for example, have they been validated or are they objective? This is important, as it influences confidence in the reported exposures. Equally important is whether the exposures were assessed in the same manner within groups and between groups. This question pertains to bias resulting from exposure misclassification (i.e., exposure ascertainment).

For example, a retrospective self-report of dietary salt intake is not as valid and reliable as prospectively using a standardized dietary log plus testing participants' urine for sodium content because participants' retrospective recall of dietary salt intake may be inaccurate and result in misclassification of exposure status. Similarly, BP results from practices that use an established protocol for measuring BP would be considered more valid and reliable than results from practices that did not use standard protocols. A protocol may include using trained BP assessors, standardized equipment (e.g., the same BP device which has been tested and calibrated), and a standardized procedure (e.g., patient is seated for 5 minutes with feet flat on the floor, BP is taken twice in each arm, and all four measurements are averaged).

Question 12. Blinding of exposure assessors

Blinding or masking means that outcome assessors did not know whether participants were exposed or unexposed. To answer this question, reviewers examined articles for evidence

that the outcome assessor(s) was masked to the exposure status of the research participants. An outcome assessor, for example, may examine medical records to determine the outcomes that occurred in the exposed and comparison groups. Sometimes the person measuring the exposure is the same person conducting the outcome assessment. In this case, the outcome assessor would most likely not be blinded to exposure status. A reviewer would note such a finding in the comments section of the assessment tool.

One way to ensure good blinding of exposure assessment is to have a separate committee, whose members have no information about the study participants' status as cases or controls, review research participants' records. To help answer the question above, reviewers determined if it was likely that the outcome assessor knew whether the study participant was a case or control. If it was unlikely, then the reviewers marked "no" to Question 12. Outcome assessors who used medical records to assess exposure should not have been directly involved in the study participants' care, since they probably would have known about their patients' conditions. If the medical records contained information on the patient's condition that identified him/her as a case (which is likely), that information would have had to be removed before the exposure assessors reviewed the records.

If blinding was not possible, which sometimes happens, the reviewers marked "NA" in the assessment tool and explained the potential for bias.

Question 13. Statistical analysis

Were key potential confounding variables measured and adjusted for, such as by statistical adjustment for baseline differences? Investigators often use logistic regression or other regression methods to account for the influence of variables not of interest.

This is a key issue in case-controlled studies; statistical analyses need to control for potential confounders, in contrast to RCTs in which the randomization process controls for potential confounders. In the analysis, investigators need to control for all key factors that may be associated with both the exposure of interest and the outcome and are not of interest to the research question.

A study of the relationship between smoking and CVD events illustrates this point. Such a study needs to control for age, gender, and body weight; all are associated with smoking and CVD events. Well-done case-control studies control for multiple potential confounders.

Matching is a technique used to improve study efficiency and control for known confounders. For example, in the study of smoking and CVD events, an investigator might identify cases that have had a heart attack or stroke and then select controls of similar age, gender, and

body weight to the cases. For case-control studies, it is important that if matching was performed during the selection or recruitment process, the variables used as matching criteria (e.g., age, gender, race) should be controlled for in the analysis.

General Guidance for Determining the Overall Quality Rating of Case-Controlled Studies

NHLBI designed the questions in the assessment tool to help reviewers focus on the key concepts for evaluating a study's internal validity, not to use as a list from which to add up items to judge a study's quality.

Internal validity for case-control studies is the extent to which the associations between disease and exposure reported in the study can truly be attributed to the exposure being evaluated rather than to flaws in the design or conduct of the study. In other words, what is ability of the study to draw associative conclusions about the effects of the exposures on outcomes? Any such flaws can increase the risk of bias.

In critical appraising a study, the following factors need to be considered: risk of potential for selection bias, information bias, measurement bias, or confounding (the mixture of exposures that one cannot tease out from each other). Examples of confounding include co-interventions, differences at baseline in patient characteristics, and other issues addressed in the questions above. High risk of bias translates to a poor quality rating; low risk of bias translates to a good quality rating. Again, the greater the risk of bias, the lower the quality rating of the study.

In addition, the more attention in the study design to issues that can help determine whether there is a causal relationship between the outcome and the exposure, the higher the quality of the study. These include exposures occurring prior to outcomes, evaluation of a dose-response gradient, accuracy of measurement of both exposure and outcome, sufficient timeframe to see an effect, and appropriate control for confounding–all concepts reflected in the tool.

If a study has a "fatal flaw," then risk of bias is significant; therefore, the study is deemed to be of poor quality. An example of a fatal flaw in case-control studies is a lack of a consistent standard process used to identify cases and controls.

Generally, when reviewers evaluated a study, they did not see a "fatal flaw," but instead found some risk of bias. By focusing on the concepts underlying the questions in the quality assessment tool, reviewers examined the potential for bias in the study. For any box checked "no," reviewers asked, "What is the potential risk of bias resulting from this flaw in study

design or execution?" That is, did this factor lead to doubt about the results reported in the study or the ability of the study to accurately assess an association between exposure and outcome?

By examining questions in the assessment tool, reviewers were best able to assess the potential for bias in a study. Specific rules were not useful, as each study had specific nuances. In addition, being familiar with the key concepts helped reviewers assess the studies. Examples of studies rated good, fair, and poor were useful, yet each study had to be assessed on its own.

Last Updated March 2014

CODING MANUAL FOR CASE-CONTROL STUDIES

SELECTION

1) Is the Case Definition Adequate?

a) Requires some independent validation (e.g. >1 person/record/time/process to extract information, or reference to primary record source such as x-rays or medical/hospital records)
b) Record linkage (e.g. ICD codes in database) or self-report with no reference to primary record
c) No description

2) Representativeness of the Cases

a) All eligible cases with outcome of interest over a defined period of time, all cases in a defined catchment area, all cases in a defined hospital or clinic, group of hospitals, health maintenance organisation, or an appropriate sample of those cases (e.g. random sample)
b) Not satisfying requirements in part (a), or not stated.

3) Selection of Controls

This item assesses whether the control series used in the study is derived from the same population as the cases and essentially would have been cases had the outcome been present.

a) Community controls (i.e. same community as cases and would be cases if had outcome)
b) Hospital controls, within same community as cases (i.e. not another city) but derived from a hospitalised population
c) No description

4) Definition of Controls

a) If cases are first occurrence of outcome, then it must explicitly state that controls have no history of this outcome. If cases have new (not necessarily first) occurrence of outcome, then controls with previous occurrences of outcome of interest should not be excluded.
b) No mention of history of outcome

COMPARABILITY

1) Comparability of Cases and Controls on the Basis of the Design or Analysis

A maximum of 2 stars can be allotted in this category

Either cases and controls must be matched in the design and/or confounders must be adjusted for in the analysis. Statements of no differences between groups or that differences were not statistically significant are not sufficient for establishing comparability. Note: If the odds ratio for the exposure of interest is adjusted for the confounders listed, then the groups will be considered to be comparable on each variable used in the adjustment. There may be multiple ratings for this item for different categories of exposure (e.g. ever vs. never, current vs. previous or never)
Age =☆ , Other controlled factors =☆

EXPOSURE

1) Ascertainment of Exposure

Allocation of stars as per rating sheet

2) Non-Response Rate

Allocation of stars as per rating sheet

References

US-Department of Health and Human Services, National Heart, Lung and Blood Institute. Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (2014). URL: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (Zugriff: 04.07.2016)

US-Department of Health and Human Services, National Heart, Lung and Blood Institute. Quality Assessment of Case-Control Studies (2014).
URL: https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/cohort (Zugriff: 04.07.2016)

Wells et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. The Ottawa Hospital. Research Institute.
URL**:** https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/case-control (Zugriff: 04.07.2016)

Part II

Table A1a: Primary research articles presenting methods and results of UFP/ Quasi-UFP epidemiologic short-term studies, mortality

Reference	Country, City	Study period	Study Design	Sample Size, Main study population	Exposure Assessment	Size Fractions[a]	Tech. Device	Covariate adjustment	Outcome Assessment	Outcome	Exposure time window[b]	Effect sizes (confidence intervals) per increment
Time-series												
Lanzinger et al. (2016a) UFIREG study	4 Cities in Germany, Czech Republic, Slovenia, Ukraine,	01/2011 - 03/2014, city-specific times overlapping	Time-series	2,582,000 General population >1 year	Measurement: Central site	PNC 20-100 (UFP), PNC 20-800	Differential or Scanning MPS	Time-trend, DoW, public holidays, vacation periods, influenza periods, T, RH	Official registry	Natural mortality	ma0-1, ma0-5, ma2-5	Percent changes in RRs/ PNC20-100 per 2,750/ml ma0-1: 0.1 (-2.0; 2.4) ma2-5: -1.2 (-4.0; 1.8) RRs/ PNC20-800 per 3,675/ml ma0-1: -0.2 (-2.4; 2.1) ma2-5: -1.2 (-4.1; 1.8)
									Official registry	CV mortality	ma0-1, ma0-5, ma2-5	RRs/ PNC20-100 per 2,750/ml ma0-1: -0.5 (-3.6; 2.8) ma0-5: -0.2 (-5.5; 5.4) RRs/ PNC20-800 per 3,675/ml

												ma0-1: -0.7 (-3.9; 2.5) ma0-5: -0.1 (-5.8; 5.9)
									Offi-cial regis-try	Resp. mortal-ity	ma0-1, ma2-5, ma0-5	RRs/ PNC20-100 per 2,750/ml ma0-1: 3.7 (-5.8; 14.2) ma0-5: 9.9 (-6.3; 28.8) RRs/ PNC20-800 per 3,675/ml ma0-1: 1.5 (-8.0; 12.1) ma0-5: 5.6 (-8.3; 21.7)
Leitte et al. (2012)	China, Beijing	03/2004 - 08/2005	Time -se-ries	8,000,000 Beijing residents, for respir-atory dis-ease adults > 20 yrs	Measure-ment: Central site	PNC3–10, PNC10–30, PNC30–50, PNC50–100, PNC100–300, PNC300–1,000 PNC3 –1 µm (NCtot) 3–100 (UFP)	TDMPS and TSI	Seasonal pattern, T, DoW	Offi-cial regis-try	Resp. mortal-ity	lag0, lag1, lag2, ma0-3, ma0-4	Percentage change/ PNC300–1,000 per 840/ml lag1: 2.1 (-3.0; 7.5) lag2: 0.7 (-3.8; 5.3) ma0-4:.11.5 (3.0; 20.7) PNC 3-100 per 13,000/ml lag1: -3.1 (-9.5; 3.9) ma 0-4: 3.9 (-7.3; 16.4)

												PNC total per 14,000/ml lag1: 0.3 (-7.5; 8.7) lag2: 9.3 (1.3; 17.9)
Meng et al. (2013)	China, Chen-yang	12/2006 - 11/2008	Time -se-ries	NR/ total popula-tion General popula-tion	Measure-ment: Central site	PNC250–280, PNC280–300, PNC300–350, PNC350–400, PNC400–450, PNC450–500, PNC500–650, PNC650–1,000	Ambient Dust Monitor 365 (GRIMM)	Calendar time, cur-rent day-mean T, RH, DoW	Adm. data-base	Total mortal-ity	ma0-1	Percent change, per 63/ml PNC650-1,000 All periods, 0.12 (-0.22; 0.45) per 2,600/ml PNC250–280, 2.41 (1.23; 3.58) warm period, per 193/ml PNC450–500 2.11 (0.72; 3.49) per 2,600/ml PNC250–280 4.21 (2.43; 5.99)
									Adm. data-base	CV mor-tality	ma0-1	All periods, range, per 63/ml PNC650-1,000 0.37 (–0.10; 0.84) per 2,600/ml PNC250–280 2.79 (1.09; 4.49)
									Adm. data-base	Resp. mortal-ity	ma0-1	All periods, range, per 63/ml PNC650-1,000 0.42 (–0.59; 1.43)

												per 1,510/ml PNC300–350 0.81 (–2.33; 3.96)
Samoli et al (2016a) Clearflo	UK, London	01/2011 - 12/2012	Time-Series	Approximately 9 million (>700/day)	Measurement: Central site	PNC<3000	CPC model 3022	Trend, DoW, public holidays, T, RH	Medical records	Total non-accidental mortality ICD-10 chapters A–R	lag1	Percent changes per 5,180/ml -0.06 (-1.16; 1.06)
									Medical records	CV mortality	lag1	-2.04 (-3.94; -0.10)
									Medical records	Resp. mortality	lag2	-1.86 (-4.50; 0.86)

Stafoggia et al. (2017) UF& HEALTH Study	8 Cities/ Areas in Finland, Sweden, Denmark, Germany, Italy, *Spain*, Greece	01/1999 - 12/2013	Time-series	12,000,000 General population	Measurement: Central site	Athens, Copenhagen, Helsinki: 0-100, Barcelone: 5-1,000, Ruhr Area: 14-750, Augsburg: 7-3,000/ 10-2,000, Stockholm: 4-3,000/ 7-3,000	Various (eTable 1; http://links.lww.com/EDE/B142	Longterm and seasonal time trends, DoW, population dynamics due to summer vacation and holidays, influenza peaks, T	Official registry	Non-accid. ICD-10 codes: 1-799	lag 0-10 shown in table: lags 5-7, figure 1: all lags	Percent increases PNC per 10,000/ml lag5: 0.32 (-0.08; 0.73) lag6: 0.35 (-0.05; 0.75) lag7: 0.37 (-0.03; 0.78) lags0-4, 8-9, range: 0.00--0.35, lag10 similar to lag 7
										CV mortality	lag0-10	Range: -0.58 (lag 0/ lag 9)to 0.45 (lag 7) no estimate significant.
										Resp. mortality	lag0-10	range: -0.6 (lag 1, lag 0 similar) to 0.65 (lag 6, lag 10 similar) significant protective estimate at lag 3 (estimate not visible in figure)

Su et al. (2015)	China, Beijing	05/2008 - 12/2008	Time-series	12,299,000 General population	Measurement: Central site	PNC3-10, PNC10-30, PNC30-50, PNC50-100, PNC3-100 (UFP)	TDMPS	T, RH, DoW, public holidays, three specific periods, heating period, season.	Official registry	CV mortality ICD10: I00–I99	lag0, lag1, ma0-5	Percent increase per 1,758/ml PNC 30-50: lag0: 2.3 (-2.1; 6.8), lag1: 6.0 (1.7; 10.6), ma0-5: 7.4 (2.1; 12.9) per8,328/ml PNC3-100: lag0: 3.7 (-1.5; 9.1), lag1: 5.7 (0.8; 10.7), ma0-5: 8.8 (2.7; 15.2)
										IHD[c]: ICD10: I20–I25,	lag 0, lag 1, ma0-5	Percent increase Per 1,304/ml PNC30-50: lag0: 2.4 (-3.9; 9.2), lag1: 2.2 (-4.0; 8.8), ma0-5: 5.7 (-1.9; 14.0) per 8,328/ml PNC3-100: lag0: 2.7 (-4.7; 10.7), lag1: -0.7 (-7.4; 6.5), ma0-5: 4.4 (-4.2; 13.8),

										Cerebro-vascular: ICD10: I60–I69	lag0, lag1, ma0-5	Percent increase Per 3,502/ml PNC30-50: lag0: 3.3 (-3.5; 10.7), lag1: 10.3 (3.3; 17.8), ma0-5: 7.5 (-0.8; 16.5) per8,328/ml PNC3-100 lag0: 8.0 (0.4; 17.0) lag2: 13.6 (5.7; 22.1) ma0-5: 13.3 (3.4; 24.2)
Wolf et al. 2015	Ger-many, Augs-burg	1999-2009	Time -se-ries	15,417 General popula-tion	Measure-ment: Central site	PNC10-2,000	CPC, TDMPS	Time trend, tempera-ture, sea-son, day of week	Offi-cial regis-try	MI and coronary deaths, fatal events	lag0, lag1, ma0-5	Percent change in RR per 6,800/ml (PNCm+f) lag0: 1.3 (-2.0; 4.7) lag1: 0.5 (-2.8; 4.0) ma0-5: -0.5 (-4.2; 3.3)

[a] Diameter size ranges are nanometers if not otherwise stated.

[b] Lags and mean averages refer to days if not otherwise stated.

[c] CPC: Condensation particle counter, DoW: Day of week, ICD: International Classification of disease, IHD: Ischaemic heart disease, ma: mean average, MI: Myocardial infarction, PNC: Particulate number concentration, RH: Relative humidity, TDMPS: Twin Differential Mobility Particle Sizer, T: Temperature.

Purple color: estimates originate from figures

Table A1b: Primary research articles presenting methods and results of UFP/ quasi-UFP epidemiologic short-term studies, morbidity

Reference	Country, City	Study period	Study Design	Sample Size, Main study population	Exposure Assessment	Size Fractions [a]	Techn. device	Covariate adjustment	Outcome	Outcome Assessment	Exposure time windows [b]	Effect sizes (confidence intervals) per increment
Case-crossover												
Cole-Hunter et al. (2013)	Australia, Brisbane	Not reported / no reference given	Case-crossover	35, healthy cycling adults, Mean age: 39	Measurement: Mobile	PNC <100 PD 1-300	Aerasense NanoTracer	NA	Nose irritation throat irritation Other symptoms, e.g. cough	Self-reported	-	Mean ± SD high vs. low inbound exposure: Nose irritation 1.82 ± 0.33 versus 1.53 ± 0.23 Throat irritation 2.00 ± 0.40 vs.1.56 ± 0.24 Cough 1.62 ± 0.26 vs. 1.26 ± 0.16
Link et al. (2013)	USA, Boston (Massachussets)	09/2006 - 06/2010	Case-crossover	176 adults >18 yrs with prior implantation of dual (atrial + ventricular) chamber ICD	Measurement: Central site	Total	CPC	T, dew point	Events of atrial fibrillation	Other	ma0-2h, ma0-6h, ma0-12h, ma0-24h, ma0-48h	Percent change ma0-2h: 24% (-4%; 61%) per 10,900/ml ma0-24: 12% (-19%; 56%) per 8,400/ml

Cohort												
Mehta et al. (2015) Veterans Affairs Normative Aging Study	USA, Boston (Massachussets)	1995-2007	Cohort	987, elderly men	Measurement: Central site	Total	CPC 3022A	Age, education, race, physical activity, seasonality, DoW, T, Anti-depressant medic.	Perceived stress during previous week (PSS-score)	Standardized-clinical examinations	ma1 week	ß-estimate per 15,997/ml PNC 3.2 (2.1; 4.3)
Wang et al. (2014) MOBILIZE[e] Boston study	USA, Boston (Massachussets)	2005-2010	Cohort	1,314 baseline. and 732 follow-up, adults, ≥ 65 yrs, mean age: 78 yrs	Measurement: Central site	NR	NR	Age, sex, race/ethnicity, visit, dew point, T, barom. pressure, DoW, season, long-term temporal trends	CESD-R ≥ 16	Standardized Interview	ma 1, 2, 3, 5, 7, 14	OR per 6,630/ml PNC lag14:1.04 (0.68; 1.57)
Panel (repeated measure)												

Karakatsani (2012)	The Netherlands, Amsterdam; Greece, Athens; UK, Birmingham; Finland, Helsinki	10/2002-03/2004	Panel (repeated measure)	136, adults ≥ 35 yrs, either asthmatic or COPD patient	Measurement: Central site	Total	CPC 3022A, TSI	Time, T, RH, DoW, medication use, individual differences in frequency of symptoms	Woken with breathing problems, Shortness of breath, Wheeze, Cough, Phlegm, Limitation of vigorous activities, Limitation of moderate activities, limitation of walking	Self-reported	lag0, lag1, lag2, ma0-6	ORs for total/asthmatic population per 10,000/ml Woken with breathing problems: lag0: 0.97 (0.87; 1.09)/1.01 (0.84; 1.21) lag1: 1.03 (0.95; 1.11)/ 1.05 (0.96; 1.14) lag2: 0.96 (0.86; 1.06)/ 1.02 (0.94; 1.11) ma0-6: 0.910 (0.64; 1.30)/ 1.20 (0.95; 1.50) Shortness of breath: lag0: 0.97 (0.90; 1.05)/0.98 (0.89; 1.06) lag1: 0.91 (0.84; 0.98)/ 0.93 (0.82; 1.05) lag2: 0.92 (0.86; 0.98)/0.95 (0.88; 1.03) ma0-6: 0.91 (0.77; 1.07)/1.03 (0.86; 1.24) Wheezing: lag0: 0.93 (0.79; 1.10)/0.98 (0.82; 1.17) lag1: 0.95 (0.82;

												1.10)/0.99 (0.82; 1.19) lag2: 0.99(0.81; 1.15)/1.05 (0.84; 1.3) ma 0-6: 1.09 (0.64; 1.87)/ 1.41 (0.73; 2.71), Cough: lag0: 0.98 (0.92; 1.05)/0.98 (0.91; 1.06) lag1: 1.01 (0.94; 1.08)/ 0.97 (0.90; 1.05) lag2: 0.97 (0.90; 1.05)/0.92 (0.81; 1.04) ma0-6: 0.89 (0.71; 1.12)/0.82(0.62; 1.1)
Scripted Exposure												
Langrish et al. (2012)	China, Bei-jing	03/2009-05/2009	Scripted Expo-sure	98, non-smoking adults, mean age: 62 yrs, history of CAD[c]	Meas-ure-ment: Mobile	Total	CPC[d] 3,007	NA	Symp-toms	Self-re-ported	2 hour walk, 24 hour study period	Group comparison: Mask use vs. no mask: The mask interven-tion reduced general symptoms signifi-cantly for cough, irri-tation of the throat, etc.
Time-series												

Wolf et al. 2015	Germany, Augsburg	1999-2009	Time-series	15,417, general popula-tion	Meas-ure-ment: Central site	PNC 10-2,000	CPC, TDMPS	Time trend, T, season, DoW	MI and coro-nary events	Official registry	lag0, lag1, ma0-5	percent change in RRs for total events per 6'800/ml lag1: 1.5 (-0.8; 3.7) lag2: 0.4 (-1.9; 2.8) ma0-5: 0.8 (-1.7; 3.4) Nonfatal events: lag1: 1.6 (-1.5; 4.8) lag2: 0.3 (-2.9; 3.6) ma0-5: 2 (-1.5; 5.8) Incident events: lag1: 0.7 (-2.1; 3.5) lag2: -0.1 (-2.9; 2.8) ma0-5: -0.2 (-3.3; 2.9) Recurrent events: lag1: 4.1 (-0.6; 9) lag 2: 3.8 (-1.1; 8.9) ma 0-5: 6 (0.6; 11.7)

[a] Diameter size ranges are nanometers if not otherwise stated.

[b] Lags and mean averages refer to days if not otherwise stated.

[c] CAD: Coronary artery disease, CESD-R: Revised Center for Epidemiological Studies Depression Scale, COPD: Chronic obstructive pulmonary disease, CPC: Condensation particle counter, DoW: Days of week, MA: Mean average, MI: Myocardial infarction, NA: Not available, NR: No reference, OR: Odds ratio, PNC: Particulate number concentration, T: Temperature, TDMPS: Twin Differential Mobility Particle Sizer.

[d] MOBILIZE: **M**aintenace of **B**alance, **I**ndependent **L**iving, **I**ntellect and **Z**est in the **E**lderly of BOSTON.

Table A1c: Primary research articles presenting methods and results of UFP/quasi-UFP epidemiologic short-term studies, emergency/hospital admissions

Reference	Country, City	Study period	Study Design	Sample Size, Main study population	Exposure Assessment	Size Fractions[a]	Tech. device	Covariate adjustment	Outcome	Outcome Assessment	Exposure time win-DoWs[b]	UFP effect sizes (conficence intervals)
Case-crossover												
Evans et al. (2014)	USA, Rochester (NY)	08/2006 - 06/2009	Case-crossover	74, asthmatic children, 3-10 yrs,	Measurement: Central site	PNC <100, AccMP[c]: 100-500	SMPS	T, RH	Number of paediatric asthma visits	Medical records	ma1, ma2, ma3, ma4, ma5, ma6, ma7	PNC/ORs ma1: 0.89 (0.64; 1.24)per 3,007/ml ma4: 1.27 (0.9; 1.79) per 2,088/ml AccMP/ORs ma1: 0.73 (0.50; 1.08) per 874/ml ma4: 1.00 (0.71; 1.40) per 638/ml
Gardner et al. (2014)	USA, Rochester (NY)	01/2007 - 12/2010	Case-crossover	338 STEMI 339 NSTEMI events	Measurement: Central site	PNC <100, AccMP: 100-500	SMPS	T, RH	STEMI/ NSTEMI Cardiac Catheterizations due to acute coronary symptom,	Medical records	lag0h, lag0-2h, lag0-11h, lag0-23h, lag0-47h, lag0-71h, lag0-95h	ORs, STEMI/ NSTEMI, PNC lag0: 1.03 (0.95; 1.12)/ 0.99 (0.90; 1.10) per 4,245/ml lag0-23: 1.06 (0.89; 1.26)/ 1.01 (0.86; 1.18) per 3,284/ml AccMP lag0: 1.07 (0.91; 1.27)/ 0.97 (0.82; 1.15) per 860/ml,

												Lag0-23: 1.12 (0.92; 1.38)/ 0.97 (0.81; 1.17) per 775/ml
Iskandar et al. (2012)	Denmark, Copenhagen	05/2001 - 12/2008	Case-crossover	8,226, children aged 0-18 years admitted in 8 specific hospitals	Measurement: Central site	PNC 10-700	DMPS	Dew point, wind speed, global radiation	Hospital admission due to asthma	Official registry	ma 5 (lag0-4)	ORs per 3,812/ml overall: 1.06 (0.98; 1.14) 0-1 year-olds: 1.08 (0.97; 1.22) 2-5 year-olds: 1.07 (0.96; 1.20) 6-18 year-olds: 1.02 (0.91; 1.15)
Rosenthal et al. (2013)	Finland, Helsinki	1998-2006	Case-crossover	2,134 (all cardiac), MI: 629, other: 1505, patients with out-of-hospital cardiac arrest, mean age: 68 yrs	Measurement: Central site	PNC <100 (UFP), 100-320 (AccMP)	DMPS	T, RH	Out-of hospital card. Arrest/ OHCA, all cardiac causes, MI, other cardiac	Adm. database	lag0h ,lag1h, lag2h, lag3h, ma07h, lag0, lag1, lag2, lag3, ma03	ORs/ all cardiac causes, UFP per 10,624/ml ma03: 0.92 (0.78; 1.09) - lag3: 1.03 (0.93; 1.15) AccMP per 1,007/ml lag2: 0.96 (0.89; 1.03) lag0: 1.04 (0.97; 1.12) ORs/ OHCA due to MI UFP per 10,624/ml: lag3: 0.97 (0.80; 1.05)

												lag0: 1.27 (1.05; 1.54) AccMP per 1,007/ml lag2: 0.96 (0.8; 1.10) lag0: 1.19 (1.04; 1.35) ORs/ OHCA due to other cardiac UFP per 10,624/ml: lag0: 0. 86 (0.75; 0.98) lag3: 1.07 (0.94; 1.22) AccMP per 1,007/ml: lag2: 0.95 (0.87-1.04) lag3: 1.04 (0.95-1.14)
Wich-mann et al. (2013)	Denmark, Copenha-gen	01/2000 - 12/2010	Case-cross-over	4,657 Patients with OHCA, mostly older than 75 yrs	Measure-ment: Central site	PNC: 10-700, PAC: 10-700, PVC: 10-700	DMPS, custom built	Public holidays, T, RH	Out-of hos-pital cardiac arrest	Adm. data-base	lag0, lag1, lag2, lag3, lag4, lag5, ma2, ma3,ma4, ma5, ma6, lag0-7h,	Estimated by figures in supplement, per-cent changes: PNC per 3,828/ml, lag4/lag5: 3.0 (-4; 10)

											ma4, ma8, ma24	lag0/ ma2/ma3/ma4/ma5 : -3 (-10; 4) PAC: range: -4.5 to + 2.5 per 155.00 µm²/m³, PVC: range: -4 - +2 per 7.14 m³/m³ increase per hourly AP levels: PNC: range: -4- +1 per 4,856/ml PAC: range: -5 - -3 per 174.71 µm²/m³, PVC: range: -6 - -4 per 7.77 µm³/m³
Time-series												
Delfino et al. (2014)	USA, California	2000-2008	Time-series	7,492 children 0-18 with a primary diagnosis of asthma, (11,177)	Dispersion	Not reported / reference given	NR	T, RH	Hospital admission/emergency dep. visits with a primary diagnosis of asthma	Medical records	lag0-7 ma1, ma3, ma5, ma7	PNC analyzed only as a mediator per cool: 1,266 particles/ml warm: 1,041 particles/ml

Diaz-Robles et al. (2014)	Chile, Temuco	08/2009 - 06/2009	Time-series	2001: 255,594 2011: 309,354 (68 visits / day), general population	Measurement: Central site	PM < 100	MOUDI, 100-NR model	T, RH, wind speed, Thermo-hygrometric index, Steadman index	Outpatient visits for respiratory illness	Medical records	lag0, lag1, lag2, lag3, lag4, lag5	RRs per 4.73 µg/m³ lag0: 1.03 (1.01; 1.06) lag1: 0.99 (0.96; 1.01) lag3: 1.01 (0.98; 1.03) lag4: 1.07 (1.04; 1.10) lag5: 1.05 (1.02; 1.08)
Lanzinger et al. (2016b)	Germany, Augsburg and Dresden; Czech Republic, Prague; Slovenia, Ljubljana; Ukraine, Chernivtsi	01/2011 - 03/2014, city-specific times overlapping	Time-series	2,582,000, general population	Measurement: Central site	PNC 20-100 (UFP) PNC 20-800 (PNC)	custom made Differential or Scanning MPS	Time-trend, T, RH, DoW, public holidays, vacation periods, influenza periods	CV. hospital adm.	Adm. database	ma0-1, ma0-5, ma2-5	Percent changes in RRs/ UFP per 2,750/ml ma0-1: -0.6 (-2.4; 1.1) ma0-5: -0.1 (-2.6 ; 2.4) ma2-5: 0.3 (-1.7; 2.4) RRs/ PNC per 3675/m ma0-1-0.6 (-2.3; 1.3) ma0-5 : 0.4 (-2.1 ; 3.0) ma2-5: 0.8 (-1.3; 2.9)
									Resp. hospital adm.	Adm. database	ma0-1, ma0-5, ma2-5	Percent changes in RRs/ UFP per 2,750/ml ma0-1: 1.5 (-3.4; 6.7)

												ma0-5: 3.4 (-1.7; 8.8) RRs/ PNC per 3,675/m ma0-1: 1.9 (-3.2; 7.3) ma0-5: 4.3 (-0.9; 9.8)
									Diabetes hospital adm.	Adm. data-base	ma0-1, ma2-5, ma0-5	Percent changes in RRs/ UFP per 2,750/ml ma0-1: 0.4 (-4.7; 5.7) ma0-5: 2.9 (-4.5; 10.9) RRs/ PNC per 3,675/m ma0-1: 0.6 (-4.7; 6.3) ma0-5: 3.9 (-3.7; 12.1)
Samoli et al (2016a) Clearflo	UK, Lon-don	01/2011 - 12/2012	Time-Series	appr. 9 million (>700/day)	Measure-ment: Central site	PNC< 3,000	CPC model 3022	trend, DoW, public holidays, T, RH	CV hospital admissions	Medi-cal rec-ords	lag1	Percent changes per 5,180/ml PNC 15-64y: 0.81 (-0.78; 2.42) 65+: -0.07 (-1.27; 1.15)
									Resp. hospi-tal admis-sions	Medi-cal rec-ords	lag2	0-14y: 1.86 (-0.28; 4.05) 15-64y: -1.14 (-2.66; 0.41) 65+: -1.09 (-2.42; 0.27)

Samoli et al. (2016b) UF Health	Denmark, Copenhagen; Finland, Helsinki; Italy, Rome, Sweden, Stockholm, Spain, Barcelona	2001-2011	Time-Series	appr. 9 million General population	Measurement: depending on site, mostly single site	B: 5-1,000, C: 6-700, H: 10-100, R: 7-3,000, S: 7-3,000/ 4-3000	B: WPCP, C: DMPS, H: ?, R: CPC, S: CPC	T, influenza periods	Resp. hospitalizations	Medical records	lag0, lag1, lag2, lag3, lag4, lag5, lag6, lag7	Percentage changes per 10,000/ml PNC lag0: -0.44 (-1.73; 0.87) lag1: -0.58 (-1.93; 0.79) lag2: -0.22 (-0.92; 0.38) lag4: 0.07 (-0.59; 0.73) lag5: 0.43 (-0.58; 1.45) lag7: -0.37 (-1.39; 0.66)
Liu et al. (2013)	China, Beijing	03/2004 - 12/2006	Time-series	15,380,000 , general population	Measurement: Central site	only PNC: PNC3-10, PNC10-30, PNC30-50, PNC50-100, PNC & mass: 100-300, 300-1000, 3-100, 3-1,000	TDMPS (TSI model 3221)	T, RH, Public holidays, season	Total CV emergency room visits	Medical records	ma0-1 ma0-10	Percentage changes, PNC 3-100 ma0-10: 7.2 (1.1; 13.7) per 9,040/ml ma0-1: 1.1 (-3.0; 5.3) per 10,340/ml PNC 3-1000 ma0-10: 5.8 (-0.5; 12.4) per 10,310/ml ma0-1: 2.2 (-2.2; 6.8) per 11,990/ml PM 3-1000 ma0-10: -0.3 (-3.2; 2.6) per 40.7 µm/m³ ma0-1: 1.4 (-1.4; 4.3) per 68.5 µm/m³

[a] Diameter size ranges are nanometers if not otherwise stated.

[b] Lags and mean averages refer to days if not otherwise stated.

[c]AccMP: Accumulation mode particles, CV: Cardiovascular, DMPS: Differential Mobility Particle Sizer, MA: Mean average, MOUDI: Micro-Orifice-Uniform-Deposit Impactor, NSTEMI: non ST-elevation myocardial infarction, OHCA: Out-of-hospital cardiac arrests, OR: Odds ratio, PAC: Particle area concentrations, PM: Particulate matter, PNC: Particulate number concentration, PVC: Particle volume concentration, RH: Relative humidity, RR: Relative risk, SMPS: Scanning Mobility Particle Sizer, STEMI: ST-elevation myocardial infarction, TDMPS: Twin Differential Mobility Particle Sizer, T: Temperature.

Table A1d: Primary research articles presenting methods and results of UFP/ quasi-UFP epidemiologic short-term Studies, Subclinical Outcomes

Reference	Country, City	Study period	Study Design	Sample Size, Main study population	Exposure Assessment	Size Fractions	Tech. device	Covariate adjustment	Outcome	Outcome Assessment	Exposure time windows	UFP effect sizes (conficence intervals)
Case-crossover												
Cole-Hunter et al. (2013)	Australia, Brisbane	Not reported/ no reference given	Case-crossover	35, healthy cycling adults, Mean age: 39	Measurement: Mobile	PNC <100 PD 1-300	Aerasense NanoTracer	NA	Peak flow rates	Self-reported	-	Mean ± SD high vs. low inbound exposure: Peak flow rates 1.28 ± 0.16 vs. 1.76 ± 0.31
Cohort studies												

Bind et al. (2016) Normative Ageing Study	USA, Boston (Massachusetts)	1995-2013	Panel-analysis within cohort study	1,112 men (veterans), mean age: 69 yrs	Measurement: Central site	PNC7-3,000	CPC, Model 3022A	T, RH, season, age, diabetes, BMI, smoking, pack-years, current use of statin, current use of AHM	SBP, DBP, HR, SDNN, LF:HF, Corrected QT, HDL, LDL,CRP, fibrinogen, CRP, ICAM-1, VCAM-1	Standardized-clinical examinations	ma28	SBP, percent changes per 13,845/ml PNC: 10^{th} percentile: 4.9 (1.4; 8.6), 90^{th} percentile: 1.2 (-1.7; 5.1), DBP, percent changes per 13,845/ml PNC: 10^{th} percentile: 3.6 (1.8; 5.6), 90^{th} percentile: 2.9 (1.7; 4.8) HR, percent changes per 13,845/ml PNC: 10^{th} percentile: -1.2 (-5; 2), 50th percentile: -0.2 (-5.5; 2.5), 90^{th} percentile: 6.8 (-3; 17) , SDNN, percent changes per 13,845/ml PNC: 10th percentile: 0.0 (-0.003; 0.003), 90th percentile: -0.03 (-0.07; 0.01), LF:HF, percent changes per 13,845/ml PNC: 10th percentile:

												0.03(-0.065; 0.12), 90th percentile: 0.08 (0.01; 0.13), Corrected QT, percent changes per 13,845/ml PNC: 10th percentile: -10 (0; -19), 90th percentile: -0.3 (-8; 7) HDL, percent changes per 13,845/ml PNC: 10^{th} percentile: -0.3 (-1.8; 8), 90^{th} percentile: 1.7 (-1.8; 3.4), LDL, percent changes per 13,845/ml PNC: 10^{th} percentile: 3.0 (-1.8; 7), 90^{th} percentile: 8.5 (4; 14), CRP, percent changes per 13,845/ml PNC: 60th percentile (levels > 2 mg/L: 0.4 mg/L (0.1; 0.7) interval. Results of other outcomes: see original article.

Mehta et al. (2014) Veterans Affairs Normative Aging Study	USA, Boston (Massachussets)	07/2007-08/2008	Cohort	370 elderly men	Measurement: Central site	7- to 3,000	CPC 3022A	Age, BMI, HDL, education, race, alcohol, smoking status/ dose, diabetes, seasonality, DoW, T, RH	Arterial stiffness (AI, AP)	Standardized-clinical examinations	m04h, ma01, ma03, ma07, ma14	AI/ percentage changes ma04h: 0.6 (-0.3; 1.7) per IQR (NR) ma01: 1.7 (0.4; 2.9) per 8,740/ml ma03: 2.2 (0.9; 3.5) per 7,874/ml ma14: 2.7 (1.3; 4.2) per IQR (NR) AP/ mmHg ma04h: 0.2 (-0.5 ; 1.1) per IQR (NR) ma01: 0.8 (0.0; 1.7) per 8,740/ml ma03: 1.2 (0.2; 2.0) per 7,874/ml ma14: 1.6 (0.6; 2.7) per IQR (NR)

Cross-sectional

Fuller et al. (2015) CAFEH	USA, Somerville / Boston, Massachusetts	clinical examinations: 08/2009-09/2010 UFP measurements:11/2009-12/2010	Cross-sectional	142 (250 samples)aged > 40 yrs	Central site, spatiotemp. model	NR	SPH site: butanol-based CPC (Model 3022A near-highway site: water-based CPC (Model 3781)	Age, education, BMI, smoking, HTM, income, DoW	IL-6 (pg/mL), hs-CRP, TNF-RII, fibrinogen	Standardized-clinical examinations	lag1, lag2, lag3, ma3, ma7, ma14, m21	Effect estimates were highest for a 28-day moving average, with 91.5% (9.4%, 235%) increase in IL-6, per 5,000 particles/ml.
								Age, BMI, employment, income, DoW, T	hs-CRP (mg/L)		lag1, lag2, lag3, ma3, ma7, ma14, ma21	Effect estimates were highest for a 28-day moving average, with a 74% (-6.6%; 223.0%) increase in hs-CRP

												Analyses using PNC concentrations at the MAC (near motorway central site) did not identify strong trends in effect estimates with the biomarkers. There was, however, a statistically significant 12.3% (-17.8%; -6.4%) decrease in hsCRP.
								Age, race, education, BMI, CHF, employment, T,	TNF-RII (pg/mL)		lag1, lag2, lag3, ma3, ma7, ma14, ma21	There were statistically significant associations for a 14-day ma with TNF-RII

								Age, education, BMI, smoking, CHF, DoW	Fibrinogen (mg/dL)		lag1, lag2, lag3, ma3, ma7, ma14, ma21	Effect estimates were highest for a 28-day moving average, with 58.7 pg/mL (-12.8%; 130.2%) increase in fibrinogen with each 5000 unit increase in the 28-day MA of PNC. MAC did not identify strong trends in effect estimates with the biomarkers.
Karottki et al. (2014)	Denmark, Copenhagen	10/2011-02/2012	Cross-sectional	Outdoor: 49, Indoor: 75, non-smoking adults, 41-68 yrs	Measurement: Central site, Measurement: Residential	Outdoor: PNC10-280, indoor: PNC10-300	CPC, DMPS	Age, sex, BMI, vasoactive drugs	MVF, lung function, inflammatory markers	Standardized-clinical examinations	lag2	Outdoor effect of PNC per 1,001/ml, percent changes: MVF: -8.9 (-15.9; -1.4), HBA1c: -1.5 (-8.1; 5.5) hsCRP: 46.5 (-10.5; 139.9) FEV1/FVC: 2.2 (-0.8; 5.3)

Ljungman et al. (2014) Framingham heart study	USA, Boston (Massachusetts)	3rd generation cohort: 2003-2005, Offspring Cohort: 2005-2008	Cross-sectional	2,072, mean age: 56 yrs,	Measurement: Central site	Total	CPC, Model 3022A	Age, sex, cohort, diabetes, BMI, triglyceride level, ratio of total cholesterol to HDL, SBP, income, education, smoking, DoW, season, time trend, T, RH, T × RH, use of statin /AHM	Peripheral arterial tonometry ratio, baseline pulse amplitude	Other	ma1, ma2, ma3, ma5, ma7	PAT ratio: No consistent pattern of association was evident between averaging periods of particle number hyperemic response Baseline pulse amplitude ma1: 12.5 (5; 21) per 15,000/ml ma5: 18.2 (8.9; 28.2) per 15,000/ml ma7: 18.4 (8.9; 28.7) per 15,000/ml
Panel (cross-sectional)												

Croft et al. (2017)	USA, Rochester (NY)	11/2011-12/2013	Panel (cross-sectional)	135, adults ≥ 18 yrs, with acute coronary syndrome	Measurement: Central site	PNC10-100 (UFP) PNC100-500 (AccMP)	3071 Electrostatic Classifier with a 3010 CPC	Age, dyslipidemia, prior MI, smoking , year, weekday, hour of the day, T, RH	CRP, Fibrinogen, MPO, D-dimer	Standardized-clinical examinations	Lag hours: 1h 12h 24h 48h 72h 96h	AccMP, percent changes 1-24h lags, most distinct estimate Fibr, 12h: 2.40 (1.30; 3.50) per 452/ml CRP, 1h: 3.17 (-0.75; 7.09) per 395/ml MPO: 12h: -2.80 (-4.68; -0.92) per 452/ml d-dimer, 12h: 0.23 (-3.25; 3.71) per 452/ml 72 and 96 h lags less distinct. UFP, percent changes CRP: 1h: 1.25 (-0.63; 3.12) per 2202/ml 12h: 3.11 (-1.40; 7.62) per 2477/ml 48-76h lags inconsistent. Fibrinogen, 12h: 2.33 (1.07; 3.59) per 2477/ml MPO, 12h: -3.28 (-5.32; -1.23) per 2477/ml
Panel (repeated measure)												

Bartell et al. (2013)	USA, Los Angeles	2005-2007	Panel (repeated measure)	50, Retirement community residents, ≥ 65 yrs, history of CAD, non-smoking, w/o exposure to ETS	Measurement: Residential	PNC5 – 3,000 $PM_{0.25}$: 0-250	CPC model 3785	Daily average actigraph-derived physical activity and heart rate, T, DoW, seasonal study phase, community group	HRV, Arrhythmia	Standardized-clinical examinations	Lags PNC 1h 8h lag0 lag1 lag2 lag3 lag5 PM0.25: lag0 (24 h), lag 1 (25–48 h), lag2	Ventricular tachycardia, per 6,351/ml PNC: RRs, daily lag0: 0.70 (0.41; 1.20), lag3: 0.42 (0.09; 1.94), lag5d: 0.20 (0.02; 1.67), ORs, hourly daytime: 1h1.06 (0.86; 1.30), 8h 0.90 (0.64; 1.26), lag3: 1.16 (0.41; 3.26), lag5: 2.43 (0.55; 10.7), hourly nighttime ORs: 1h: 0.77 (0.59; 1.01), 8h: 1.09 (0.70; 1.70), lag3: 0.70 (0.26; 1.92), lag5: 0.88 (0.10; 7.89). per 7.0 microg/m^3 PM0.25, Daily RRs 0d: 1.04 (0.67; 1.60),

												lag1: 1.20 (0.97; 1.47), lag2: 1.29 (0.73; 2.29)
Chung M. et al. (2015) CAFEH	USA, City of Somerville, the Dorchester, South Boston, MA	first visit: 08/2009-4/20111 second visit: 02/2010-06/2011	Panel (repeated measure)	220, resident near highway	Measurement: Central site	PNC < 100	CPC (Model 3022a)	Age, gender, race, income, education level, smoking, obesity, AHM, sampling method, distance to highway	SBP, DBP, PP	Standardized-clinical examinations	Daily average (24 h prior to clinic date)	ß-estimates per 10,000/ml PNC SBP: 2.19, Robust SE: 1.82, P.0.23 DBP: 2.40, Robust SE: 1.11, P: 0.03 PP: -0.16, Robust SE: 1.34, P0.91
Cole-Hunter et al. (2016)	Spain, Barcelona	02/2011-11/2011	Panel (cross-sectional)	28, healthy cycling adults	Microscale personal exposure model	PNC <100	CPC Model 3007, TSI,	BMI, ambient temperature, noise, linear and quadratic terms for HR	HRV (SDNN, rMSSD, LF, HF, LF:HF)	Standardized-clinical examinations	2 hours	Percentage changes per 10,000/ml SDNN(ms) low traffic site -4.9 (-7.1; -2.7), high traffic site: -0.52 (-0.96; -0.08), similary for RMSSD and LF and HF. Positive estimates for LF:HF e.g. at low traffic site: 1.0 (-3.1; 5.2), high traffic site: 0.17 (-0.66; 1.0)

Frampton et al. (2012)	USA, Rochester (NY)	Not reported/ no reference given	Panel (repeated measure)	19 never smokers,30–60 yrs, with T2D	Measurement: Central site	PNC 10-100	SMPS, version 3071	T, RH, order of measurement, age-group, and sex	Platelet expression of CD62P and CD40L, platelet-leukocyte conjugates, circul. MP, CD40L	Standardized-clinical examinations	lag1 lag2 lag3 lag4 lag5 lag days 1–5 combined	ß-estimates per 2,482/ml Platelet CD62P ↓ D2,4, 1–5, Platelet-Leukocyte Conjugates↓ D1,2, 1–5, Platelet CD40L ↓ D1,4, 1–5, Soluble CD40L ↑ D1 only figures and summarizing table Number of platelet-let-leukocyte conjugates decreased by -80 (-123 to -37, p=0.001) on the first lag day (20–44 hours prior to the blood draw) and by -85 (-139 to -31, p=0.005) on combined lag days 1 to 5, However, levels of soluble CD40L increased 104 (3 to 205, p=0.04) pg/ml on lag day 1, a finding consistent with prior platelet activation

Gong et al. (2014)	China, Beijing	06/2008-10/2008	Panel (repeated measure)	125, nonsmoking 22-27 yrs, working on hospital campus, most (92%) residing in dormitories of near-by university	Measurement: Central site	PNC13-108.2 AccMP: 108.3-764.7	TDMPS, CPC	T, RH, sex, DoW	HR, BP, vWF, CD40 ligand, P-selectin, FeNO, malondialdehyde, nitrite, urinary malondialdehyde, 8-hydroxy-2′-deoxyguanosine, plasma fibr., WBC	Standardized-clinical examinations	lags0-6	Percent changes per IQR (not reported) SBP/DBP: inconsistent, significant at lag4 (SBP) FeNO, lag0: 25.34% (12.96%; 39.09%) EBC pH value, lag1: 1.54% (0.79%; 2.28%) EBC nitrite, lag6: 25.64% (16.12%; 35.94%) WBC, lag 0: 4.1% (1.2%; 7%) urinary MDA, lag3 10.89% (0.56%; 22.3%) 8-OHdG, lag 5: 42.8% (18.2%; 72.6%) EBC MDA and Plasma fibrinogen showed no significant association

Hampel et al. (2012)	Germany, Augsburg	03/2007-12/2008	Panel (repeated measure)	61, with Diabetes or IGT, non-smoking, w/o cardiac disease	Measurement: Central site	PNC 10-100nm	TDMPS system consisting of two DMA.	Long-term time trend, time of day, DoW, T, RH, bar. pressure	HR, SDNN, rMSSD	Standardized-clinical examinations	1h	Percent changes per 7,157 /ml UFP were only related with lagged decreases in SDNN showing the strongest associations -1.9% [-3.4; -0.4%].

Hampel et al. (2014) KORA	Germany, Augsburg	04/2008-11/2008	Ultra-short-term panel-study	5, non-smoking, w/o history of angina pectoris, heart attack or stroke.	Measurement: Mobile	PNC 200->1000	PTRAK, Model 8525	For each outcome separately. T, RH barom. press.	HR, SDNN, RMSSD, HF, LF	Standardized-clinical examinations	Lag minutes concurrent 0-4, 5-9, 10-14, 15-19, 20-24, 25-29	No association with HR, SDNN and LF. Elevated PNC levels led to delayed reductions in RMSSD and HF. The strongest effects were observed with lags of 15–19 min, 20–24 min, and 25–29 min for RMSSD and with lags of 10–14 min, 15–19 min, 20–24 min for HF. Percent changes per 9,581/ml RMSSD, 0-4 min: -2.2 (-4.16; -0.19) 25-29 min: -4.51(-6.38; -2.61) HF, 25-29 min: 2.26 [-4.26; -0.23] 15-19 min:-3.89 [-6.08; -1.65]

Han et al. (2016)	China, Shang-hai	04/2010-09/2011	Panel (re-peated meas-ure)	55, elderly retired adults, 50-70 yrs, with T2DM or IGT	Measure-ment: Central site	PNC5.6-100.0 (UFP) PNC5.6-20.5 (AitMP) PNC100.0-560.0 (AccMP) PNC5.6-10.0 PNC10.0-20.5, PNC20.5–48.7, PNC48.7–100.0, PNC100.0–205.4 , PNC205.4–560.	FMPS, TSI	T, RH, DoW, age, Sensitive adjust-ment: gender, condition of obese, diabetes, hyperten-sion and use of medica-tion	FeNO	Standard-ized-clini-cal exami-nations	ma up to 24h	Percent changes, ma08: 9.25 (2.87; 16.03) per 8,523/ml UFP: 1.44 (-3.21; 6.31) per 3,709/ml PNCnuc 11.68 (4.90; 18.89) per 5.673/ml PNCait: 8.49 (1.71; 15.72) per 2,279/ml PNCacc
Hoff-mann et al. (2012)	USA, Boston (Mas-sa-chusse ts)	09/2006-07/2010	Panel (re-peated meas-ure)	70, non-smok-ing adults, 40-85 yrs, with T2DM	Measure-ment: Central site	Total	CPC 3022A TSI	Age, sex, BMI, HbA1c, season, T, years of diabetes, glucose, AHM	Blood pres-sure	Standard-ized-clini-cal exami-nations	ma1-5	Percentage changes in SBP: ma2: 1.6 (–0.6; 3.9) per 7,300/ml ma5: 1.1 (–1.6; 4.0) per 6,600/ml

Huttunen et al. (2012)	Finland, Kotka	11/2005-05/2006	Panel (repeated measure)	52, non-smoking adults, >50 yrs, IHD patients	Measurement: Central site	PNC>20nm	CPC 3007	Time-trend, T	interleukin (IL)-1b, IL-6, IL-8, IL-12, IFN, CRP, fibrinogen, myeloperoxidase and WBC	Standardized-clinical examinations	lag0 lag1 lag2 lag3	Percent changes per 4,841/ml Interleukin 12, lag0: 2.73 (8.15; 3.01), lag1: 2.06 (3.53; 7.98), lag3: 6.41 (0.28; 12.90) Interleukin 8, lag 1: 3.35 (-5.10; 12.55) CRP, lag1: 4.33 (-4.84; 14.38) Myeloperoxidase, lag 1: 1.29 (-1.83; 4.50) Fibrinogen, lag 1: -0.12 (-1.77; 1.5) WBC, lag1: 0.17 (-1.44; 1.78)
Karottki et al (2015)	Denmark, Copenhagen	11/2010-05/2011	Panel (repeated measure)	48, non-smoking adults, middle aged (mean age: 68)	Measurement: Central site	indoor: PNC10-300, outdoor: PNC10-280	CPC, DMPS	Age, sex, BMI, vasoactive drugs, T, season, air filtration	MVF, lung function, CRP, Leukocytes, other inflammatory markers	Standardized-clinical examinations	lag2	Percent changes of outdoor PNC per 3,000/ml: MVF: -3.4 (-6.6; -0.05), CRP: 3.4 (-6.2; 13.9) FEV1/FVC: -4.0 (-8.1; 0.5) *further outcomes view table 4 in original article

Li et al. (2016) CAFEH	Taiwan, Xinzhuang distrcit, New Taipei	02/2008-06/2008	Panel (repeated measure)	59, school children with asthma and/or allergic rhinitis	Measurement: Central site	UFP: 10-100 nm; AccMP: 100-2500 nm; TP: 10-2500 nm	SMPS (TSI); optical aerosol spectrometer (PMS)	Ozone	Spirometric indices	Standardized-clinical examinations	lag1	ß-estimates per 5,646.4/ml UFP: 0.2-0.25, significant for FEF 50% and FEF 75%, Adverse estimates only for Factor 5, secondary aerosol contributors. No significant associations of FVC with AccMP.
Manney et al. (2012) RUPIOH study	The Netherlands, Amsterdam; Greece, Athens; UK, Birmingham; Finland, Helsinki	10/2002-03/2004	Panel (repeated measure)	133, adults, ≥ 35 yrs, asthmatic or COPD patient	Measurement: Central site, Measurement: Residential	PNC >7nm	CPC 3022A, TSI	City, T, season, trend	levels of nitrite plus nitrate (NOx) in exhaled breath condensate (EBC)	Standardized-clinical examinations	lag0, lag1, lag2	Percent change per 10,000/ml PNC central site / residential outdoor lag0: -4.3 (-17.7; 11.1 / 2.9% (-8.6; 15.7) lag1: -5.1 (- 17.9; 9.8) / -4.3% (-16.6; 9.8) lag2: -14.0 (-26.6;-0.8) / -6.1% (-17.7; 7.1)

Peng et al. (2016)	USA, Boston (Massachusetts)	08/2006-07/2010	Panel (repeated measure)	70, non-smoking adults, 40-85 yrs, with T2DM	Measurement: Central site	Total	NR/ no reference given	Subject, T, water vapor pressure, season, scrubbed room NO	NO in exhaled breath (FeNO)	Standardized-clinical examinations	lag6h lag24h lag2 lag5 lag7	Percent changes per 8,270/ml lag6h: 9.86 (3.59; 16.52), in general slightly decreasing estimates with greater lags to app. 9.00 (-1; 20) at lag7.
Peters et al. (2015)	Germany, Augsburg	03/2007 - 12/2008	Panel (repeated measure)	64, non-smoking adults, mean age: 66, 32 with confirmed T2DM and 32 with IGT	Measurement: Mobile, Measurement: Personal	Personal: PNC10-1000 nm, Central: PNC10-100nm, PNC100-800nm	Personal: CPC 3007, central: TDMPS	Trend, meteorology, time of day, further adjustment for noise	HR and measures of HRV incl. SDNN	Standardized-clinical examinations	Concurrent, lag0-4 min, lag5-9 min, lag10-14 min	Percent changes per 16,000/ml personal PNC measurements: SDNN, concurrent -0.56 (-1.02; -0.09), lag0-4 min: 0.36 (-0.11; 0.83) HR, concurrent: -0.06 (-0.18; 0.07) lag0-4 min: 0.23 (0.11; 0.36) lag5-0 min: 0.16 (0.04; 0.28) RMSSD: estimates close to 0

Pieters et al. (2015) HEAPS study	Belgium, Antwert	05/2011-12/2011	Panel (repeated measure)	130, children 6-12 yrs, attending two primary schools, not exposed to ETS	Measurement: Central site	20–30 nm, 30–50 nm, 50–70 nm, 70–100 nm, 100–200 nm, > 200 nm, total	SMPS; model 3080	Sex, age, height, weight, parental education, neighborhood SES, fish consumption, HR school, DoW, season, wind speed, T, RH, season x T	BP, IL–1β	Standardized-clinical examinations	lag0	SBP, ß-estimates (mmHg): PN20-30nm: 6.35 (1.56; 11.47) per 860/ml 30–50 nm: 1.18 (0.05; 2.31), per 712/ml, 50–70 nm, 0.92 (–0.05; 1.89) per 540/ml, 70–100 nm: 0.86 (0.05; 1.68) per 358/ml, total UFP: 2.92 (0.30; 5.61) per 1,666/ml IL-1ß: 20-30nm: 24.20 (4.83; 47.16) 30-50 nm: 4.27 (–0.56; 9.35) 50-70 nm: 3.79 (–0.30; 8.05) 70-100 nm: 3.28 (0.33; 6.31) 100-200nm: 1.40 (0.13; 2.68) >200nm: 1.98 (–0.48; 4.49) total UFP: 2.92 (0.30; 5.61)

Rich et al. (2012)	USA, Rochester (NY)	06/2006-11/2009	Panel (repeated measure)	76, with previous MI or unstable angina	Measurement: Central site	PNC10-100 (UFP) PNC100-500 (AccMP)	Wide range particle spectrometer (model 1000XP)	Visit number, calendar time since the beginning of the study for each participant, month of year, hour of day.	Preexercise resting period: Mean NN, SDNN, rMSSD, QTc, TpTe; whole session: Mean NN, SDNN, rMSSD, HRT, DC; preexercise meas. CRP, fibrinogen, WBC, BP	Standardized-clinical examinations	0-5h, 0-23h, 24-47h, 48-71h, 72-95h, 96-119h	ß-estimates, pre-exercise resting period: MeanNN or SDNN: no clear pattern, rMSSD: AccMP (similar but less distinct pattern for UFP) : 0-5 h:-3.65 ms (–6.39; –0.91) per 897/ml 0-23h: -4.33 msec (–7.27; –1.38) per 838/ml QTc duration: no pattern, TpTe (msec): 0-23h: 0.78 msec (0.02; 1.53) per 897/ml 24-47h: 1.05 msec (0.28; 1.82) per 897/ml SBP: increase for UFP per 2,680/ml & AccMP per 897/ml at almost all lags, of which, the largest were significant 0.89 mmHg (95% CI: 0.06, 1.72) and 0.94 mmHg (95%

												CI: 0.02; 1.87) increases associated with IQR increases in UFP lagged 24–47h. Fibrinogen, per 2,680 particles/ml UFP lag 24-48h: 0.08 (0.02; 0.14) per 897/ml AccMP: lag 24-48h: 0.12 (0.04; 0.20) Other outcomes: see original article.

Rückerl et al. (2014)	Germany, Augsburg	03/2007-12/2008	Panel (repeated measure)	274, T2DM: 83, IGT: 104, genet. susc.: 87, non-smoking adults, mean age: 62 yrs	Measurement: Central site	PNC3–10, PNC10–30, PNC30–50, PNC50–100	TDMPS	T, RH, Pressure, weekday	CRP, interleukin (IL)-6, soluble CD40 ligand (sCD40L), fibrinogen, myeloperoxidase (MPO), and plasminogen activator inhibitor-1 (PAI-1)	Standardized-clinical examinations	lag0, lag1, lag2, lag3, lag4, ma5	Percent changes in the panel of T2DM or IGT CRP, PNC3-100nm lag 3: 11.7 (3.0; 21.1) per 5,722/ml ma 5: 12.2 (2.1; 23.3) per 4,279/ml: PNC3–10 nm, ma5: 5.8 (0.7; 11.1) per 390/ml PNC30–50: lag 3: 10.9 (2.2; 20.4) per 1,748/ml MPO PNC3-100nm: ma 5: 5.8 (0.7; 11.1) per 4,279/ml: PNC30–50 nm, ma 5:6.0 (0.9; 11.4) per 1251/ml PNC50–100 nm: ma 5: 5.8 (1.6; 10.1) per 1546/ml sCD40L, PNC3–10 nm lag 0h: 7 (1.1; 13.2) per 481/ml Results for PAI-1, IL6, Fibrinogen see table D1.1

Rückerl et al. (2016) KORA	Germany, Augsburg	03/2007-12/2009	Panel (repeated measure)	274, T2DM: 83, IGT: 104, genet. susc.: 88, non-smoking adults, mean age: 62 yrs,	Measurement: Central site	PNC3–10, PNC10–30, PNC30–50, PNC50–100, LC(EAD), LC10-800, LC3–10, LC10–30, LC30–50, LC50–100, SC(DCPS), SC10–800, SC3–10, SC10–30, SC30–50, SC50–100	LC(EAD): electric aerosol detector (EAD, model 3070 A), Active surface of the particles, SC(DCPS): Diffusion Charging Particle Sensor (DCPS) (model LQ1)	T, RH, Pressure, weekday	CRP, interleukin (IL)-6, fibrinogen, myeloperoxidase (MPO)	Standardized-clinical examinations	lag0, lag1, lag2, lag3, lag4, ma5	Percent change CRP PNC10–30 nm, lag 3: 13.1 [3.3; 23.8] PNC50–100 nm lag 3: 9.6 [1.8; 18.9] per 0.3 mm/cm³ LC(EAD), lag 1: 6.6 (0.1; 13.6) ma 5: 8.7 (0.3; 17.8) per 0.00 mm/cm³ LC3-10nm, ma 5: 11.7 (2.5; 21.7) per 22.3 mm2/cm³ SC(DCPS) ma 5: 29.8 [15.9; 45.3] per 168.9 mm²/cm³ SC10-800, ma 5: 9.2 (0.8; 18.3) per 0.06 SC3-10nm, ma 5: 9.6 (1.9; 18.0) per 5.7 SC30-50nm, ma 5, 3.2 (-3.9; 10.9) per 24.7 SC50-100nm, ma 5, 4.2 (-2.5; 11.4), similar pictures with significant estimates for MPO,

											IL-6 less significant, for fibrinogen in some lags significant. In general, estimates for genetically susceptible higher and more often significant.

Sarnat et al. (2014)	USA, Atlanta	2009/12-2011/04	Panel (repeated measure)	42, 21 asthmatics & 21 healthy non-asthmatics	Microscale personal exposure model	Not reported/ no reference given	CPC model 3007	Noise, cortisol level	HRV (HR, SDNN, rMSSD), CRP, eNO, FEV1, FVC, MDA	Standardized-clinical examinations		At measurement time points within 3 h after the commute, we observed mild to pronounced elevations relative to baseline in exhaled nitric oxide, CRP, and exhaled malondialdehyde, indicative of pulmonary and systemic inflammation and oxidative stress initiation, as well as decreases relative to baseline levels in the time-domain heart-rate variability parameters, SDNN and rMSSD, indicative of autonomic dysfunction. FEV1 levels were slightly elevated relative to baseline levels among asthmatic subjects at the 1 h and 2 h post-commute time points, the frequency-domain heart-rate

												variability parameter or other systemic biomarkers of vascular injury. Water soluble organic carbon was associated with changes in eNO at all postcommute time-points ($p<0.0001$).

Song et al. (2013a)	South Korea, Inchon City	03/2009-06/2009	Panel (repeated measure)	84, 41 with eczema and 43 healthy children, 8-12 yrs, without ETS at home	Measurement: Central site	PM1 PNC11-101 (UFP) PNC111-930 (AccMP)	SMPS+C comprising a DMA and a CPC (UFP & AC-CMP), multi-channel (31 different sizes, 0.25–32 µm) aerosol spectrometer (PM1)	Age, gender, height, DoW, linear time trend, T, RH (lag 1)	Peak expiratory flow rates (PEFR)	Standardized-clinical examinations	lag1 ma1-3	PEFR changes, PM1, children with AD/ without AD ma 1:-2.71 L/min (-4.81; -0.61) /-0.26 (-2.15; 1.60) per 34.1 µg/m³ ma 3: -2.42 (-4.18; -0.65) / -0.36 (-1.91; 1.18) per 19.4 µg/m³ AccMP, children with AD /without AD ma 1: -1.90 (-4.56; 0.76)/ 0.88 (-1.46; 3.21) per 7,100/ml ma 3: -1.27 (-5.35; 2.80)/ -2.01 (-5.48; 1.46) per 5,370/ml UFP, children with AD/ without AD ma 1: -1.17 (-3.81; 1.47)/ 1.65 (-0.66; 3.95) per 28,140/ml ma 3: 1.91 (-1.66; 5.48)/ -2.00 (-5.05; 1.06) per 17,680/ml

Song et al. (2013b)	South Korea, Inchon City	04/2009-06-2009	Panel (repeated measure)	84, 41 with eczema and 43 healthy children, 8-12 yrs, without ETS at home	Measurement: Central site	PM1 PNC11.1–101 nm (UFP), PNC111-454	SMPS+C comprising a DMA and CPC (UFP & AC-CMP), amulti channel (31 different sizes, 0.25–32 µm) aerosol spectrometer (PM1)	Age, BMI, passive smoking, temperature on the previous day and time trend (sampling date)	Urinary 8-OHdG levels	Standardized-clinical examinations	lag1, lag2, lag3	Percent changes PM1, Children with eczema/ without eczema lag1: 4.51 (-1.83; 11.26)/ 0.91 (-5.36; 7.58) per 31.84 µg/m³ lag2: -4.48 (-9.50; 0.79)/ -0.06 (-5.49; 5.67) per 31.21 µg/m³ lag3: -3.58 (-9.78; 3.06)/ 3.73 (-2.91; 10.81) per 31.46 µg/m³ PNC0.1-0.5, Children with eczema/ without eczema lag1: 5.96 (0.15; 12.10)/ -0.92 (-7.02; 5.58) per 5.49/ml lag2: 4.11 (-2.68; 11.38)/ 8.14 (1.13; 15.63) per 5.32/ml lag3: 1.38 (-8.23; 12.00)/ 11.32 (0.58; 23.20) pper 5.51/ml PNC0.01-0.1, children with eczema/ without eczema lag1: 5.65 (1.31; 10.18)/ 1.99 (-

												2.93; 7.16) per 32.30/ml lag2: 6.62 (0.12; 13.54)/ 13.37 (4.74; 22.71) per 32.29/ml lag3: 2.77 (-2.24; 8.02) 5.87 (-3.71; 16.41) per 32.30/ml

Sun et al. (2015)	China, Shanghai	04/2010-10/2010	Panel (repeated measure)	53, Elderly retired adults, 50-70 yrs, with T2DM or IGT	Measurement: Cen ral site	PNC5-560 nm	Fast Mobility Particle Sizer Spectrometer (FMPS Model 3091)	Age, gender, BMI, visit, DoW, T, RH	HRV (SDNN, rMSSD, LF, HF)	Standardized-clinical examinations	ma1h, 4h, 12h, 18h, 24h	Percent change in SDNN, ma4h: PNC5-560: -7.9 (-9.7; -6.1) PNC 10-20: -7 (-8.9; -5.1) PNC 20-50: -6.6 (-8.1; -5) PNC 50-100: -5.4 (-7.3; -3.4) PNC 100-200: -3.0 (-4.6; -1.3) PNC 200-560: -0.45 (-2.43; 1.56). Other lag hours less positive, with positive estimates at ma 18h and ma 24h. Similar association patterns are observed for other HRV measures, including the root mean square of successive differences between adjacent normal cycles (rMSSD), low frequency (LF) (0.04; 0.15 Hz) and high frequency (HF) (0.15; 0.4 Hz), whereas the mag-

											nitude of reduction for frequency-domain measure LF and HF were greater IQRs not reported

Wang et al. (2016)	USA, Rochester (NY)	06/2006-11/2009	Panel (repeated measure)	76, postinfarction nonsmokers patients with MI or unstable angina	Measurement: Central site	PNC10-100 nm (UFP) PNC100-500 nm (ACCMP)	Wide range particle spectrometer (model 1000XP)	T, calendar time since the beginning of the study, indicator variables for visit number, month of year, and hour of day.	CRP, fibrinogen, SBP, and T-wave complexity, SDNN, rMSSD	Standardized-clinical examinations	lag0-5h, lag 0-23h, lag 24-47h, lag 48-71h, lag 72-95h, lag 96-119h, lag 0-23h, lag 24-47h, lag 0-23h	ß-estimates per IQR (0.87 log particles/ml (6-hour mean) and 0.81 log particles/ml (24-hour) mean log UFP & 1.21 log particles/ml (6-hour mean) and 0.99 log particles/ml (24-hour mean) log AccMP SBP: lag0-23h: 1.38 (0.07; 2.68) lag24-47h: 1.60 (0.32; 2.89) AccMP and per 0.99 log particles/ml (24-hour mean) lag0-23h: 1.48 (0.09; 2.86) lag24-47: 0.61 (-0.89; 2.11) CRP: values close to zero, e.g.: 0-23h: UFP, 0.039 (-0.024; 0.102), AccMP: 0.051 (-0.017; 0.119), Fibrinogen: 0-23h:UFP: 0.04 (-0.03; 0.11), AccMP: 0.06 (-0.02;

												0.13), 24-47h, UFP: 0.07 (0.00; 0.14), Ac-cMP: 0.10 (0.02; 0.18), rMSSD, 0-23h, UFP: -3.71 (-7.18; -0.25), Ac-cMP: -1.95 (-5.64; 1.74), 72-95h, UFP: -7.48 (-10.77; -4.20), Ac-cMP: -3.54 (-7.02; -0.06), SDNN, 0-23h, UFP: -1.14 (-4.00; 1.71), Ac-cMP: -1.05 (-4.10; 2.01), Log T wave com-plexity, 0-23h, UFP: -0.042 (-0.102; 0.017), AccMP: -0.059 (-0.123; 0.005)

Wittkopp et al. (2013)	USA, Los Angeles	Not reported/ reference given	Panel (repeated measure)	38, non-smoking adults > 65 yrs with coronary artery disease	Measurement: Retirement communities	PM >250 AccMP; 250-2,500	Teflon Filters	Respiratory, urinary tract or other infections during week of biomarker measurements	CRP, TNF-alpha, soluble TNF-alpha receptor II, IL-6, soluble IL-6 receptor	Standardized-clinical examinations	ma1-9	$PM_{0.25}$: IL-6 and TNF-alpha non-significantly positive associated, positive associations of IL-6 with 3-day and 5-day $PM_{0.25}$ averages TNF-alpha was positively associated with UFP ß-estimates, IQR/$PM_{0.25}$: 5.28 (mg/m3), CRP, lag1: 91(-287,469), ma5: -156(-741,429)
Wu et al. (2012)	Taiwan, Taipei county, Sin-Jhuang	02/2007-03/2007	Panel (repeated measure)	17, non-smoking mail carriers	Measurement: Mobile	PM < 0.25µm $PM_{0.25\text{-}1\mu m}$	Personal cascade impactor sampler	Age, BMI, SHS, T during working period.	rCAVI, SDNN, rMSSD, HF, LF, LF/HF	Standardized-clinical examinations	mail delivery	Percent change per 15.3 µg/ml PM0.25, SDNN: -4.7 (-14.5; 6.2), rMSSD: -5.1 (-12.4; 3.0), HF: -5.7 (-16.5; 6.5), LF: -4.8 (-15.1; 6.8), LF/HF: 1.0 (-2.8; 5.0) rCAVI: -2 (-50; 1.0)

Za-nobetti et al. 2014	USA, Boston (Mas-sa-chusse ts)	2006-2009	Panel (re-peated meas-ure)	64, non-smok-ing adults, 49-85 yrs, with T2DM	Measure-ment: Central site	Total	CPC 3022A TSI	BAD at baseline, PM2.5, BC, sea-son,	Endo-thelial func-tion	Standard-ized-clini-cal exami-nations	ma0-5	Change in mm: -0.02 (-0.1; 0.07) IQR: 8.180/ml for 24-hour mean

Zhang et al. (2013)	China, Beijing	06/2008-10/2008	Panel (repeated measure)	125, non-smoking young adults	Measurement: Central site	SMPS: PNC14.1-736 TDMPS: PNC13-764.7	SMPS (post-Olympics), TDMPS (pre/during Olympics)	Sex, T, RH, period, DoW	HR, HRV,	Standardized-clinical examinations	lag0-6	Percent changes per 6,572/ml HR: positive associations for most lag days, although statistical significance was observed only at lag day 3 (0.5%). HRV: similar to HR, not significant: SDNN: inconsistent pattern rMSSD: significant negative associations at lag days 0 and 3 LF, HF, LF/HF no clear pattern Blood Pressure: inconsistent patterns Fibrinogen: inconsistent Red blood cell counts: signif. Negative/protective associations WBC signif. Negative/protective and positive associations Urinary HcG: 24.7% at lag3. FeNO: significantly

												and positively associated at most lags Other outcomes: see original article

Zhang et al. (2016a)	USA, Los Angeles Canada, Anaheim	2012-2014	Panel (repeated measure)	97, elderly (>65) non-smoking men, w/o psychiatric disorders, renal failure, active cancer, acute infections	Measurement for PM: 2 monitoring sites	$PM_{0.18}$, $PM_{0.18-2.5}$ (AccMP)	MOUDI, model 100-1, MSP Minneapolis	Heat index, exercise, food intake, sugar/ fat intake, use of gas stoves, trend	EBC, MDA, FeNO, oxLDL, IL-6	Standardized-clinical examinations	ma5	Percent changes, FeNO: stronger estimated associations for ultrafine PM0.18 than larger size-fractions for total mass PM 0.18: 3.0 (0.7; 5.3) per 1.1 µg/m³ AccMP: -0.8 (-3.5; 1.9) per 4.0 µg/m³ (various outcomes (elements and PAHs in $PM_{0.18}$) in figure 1&2 and supplementary tables) MDA: positively associated with total $PM_{0.18}$ mass
Zhang et al. (2016b)	USA, Los Angeles (California)	07/2012-02/2014	Panel (repeated measure)	93, elderly men	Measurement: Central site	$PM_{0.18}$, $PM_{0.18-2.5}$ $PM_{2.5}$-PM_{10}	MOUDI, model 100-1, MSP Minneapolis	Heat index, exercise, food intake, use of gas stoves	Reactive hyperemia index (RHI)	Standardized-clinical examinations	ma5	RHI slightly adversely/ not significantly associated with 5-day total mass of $PM_{0.18}$ or $PM_{0.18–2.5}$, IQR: 1.13 µg/m3

Scripted exposure

Bos et al. (2011)	Belgium, Brussels	Not reported/ no reference given	Scripted Exposure	35, physically fit, non-asthmatic adults, mean age: 43 yrs, 26% women	Measurement: Mobile	Total	P-Track UFP Counter (TSI Model 8525)	NA	BDNF (brain-derived neurotropic factor)	Standardized-clinical examinations	20 min cycling versus filtered room	Serum BDNF concentrations increased significantly after cycling in the clean room ($p = 0.02$). In contrast, BDNF serum concentrations pre/post cycling along the Antwerp Ring did not differ significantly ($p = 0.42$). Baseline values of BDNF (before cycling) did not differ significantly between the clean room test and the road trial ($p = 0.07$). Comparison of the values post-cycling did not show any significant differences

Bos et al. (2013)	Belgium: Brussels/ Mol	02/2011-05/2011	Scripted exposure	24, untrained healthy participants	Measurement: Mobile	PNC20-1,000	TSI P-TRAK UFP Counters	NA	eNO, BDNF, leukocyte, neutrophil, lymphocyte, eosinophil, monocyte, basophil counts	Other, Standardized-clinical examinations	12 week aerobic training program	eNO levels, urban group: increased significantly, Z = -2.87, P = 0.002, in the urban group, whereas eNO levels did not change, Z = -0.7, P = 0.52, in the rural group. Leukocyte count, urban group increased significantly, t(13) = j2.61, P = 0.02, whereas it did not differ significantly over time in the rural group, t(8) = 0.76, P = 0.47, BDNF levels: no group differences before, U = 54, P = 0.45, and after, U =60, P = 0.68, Cognitive testing: Reaction times on the Stroop task improved in the rural group (P = 0.001), but not in the urban group.

Jarjour et al. (2013)	USA, Berk-erley	04/2011-06/2011	Scripted expo-sure	15, healthy, never-smoking regular cy-clists, 23-48 yrs	Measure-ment: Personal	PNC 10 - 1,000	CPC	NA	Lung func-tion	Standard-ized-clini-cal exami-nations	Post-ride & 4h fol-low-up differ-ence to baseline	Average changes in lung function ranged from -0.1 liters (low-traffic post-ride FEF25-75%) to +0.24 li-ters (high-traffic 4-hour FEF25-75%), but all changes in lung function measurements were clinically in-significant, and none of the paired t-tests (by subject) for low-traffic and high-traffic lung function changes had significant p-values.

Janssen et al. (2015), RAPTES study	The Neth-er-lands, Utrecht	03/2009-11/2009	Scripted Expo-sure	31, healthy non-smok-ing stu-dents	Measure-ment: Mobile	Total	CPC	FeNO, FVC, FEV: T, RH, season, pollen counts, Resp.in-fections NAL: T, RH, sea-son, en-dotoxin.	FeNO, lung func-tion; IL-6, pro-tein /lac-toferr-in in NAL; IL-6/ hCRP, Fibrin., vWF, tPA/P AI-1 in plat.	Standard-ized-clini-cal exami-nations	2h	Percent change per 23,000/ml after excluding un-derground: FeNO: appr. 13.0 (6.0; 21.0) in-crease IL-6 (nasal): appr 15.0 (-11; 50) When the under-ground site was included in the analysis, FeNO and NAL IL-6 were con-sistently associ-ated with PNC.

Langrish et al. (2012)	China, Beijing	03/2009-05/2009	Scripted Exposure	98, non-smoking adults, mean age: 62 yrs, history of CAD	Measurement: Mobile	Total	CPC 3007	NA	BP, HR, and 12-lead electrocardiography	Standardized-clinic. examination, Self-reported	2h prescribed walks	Group comparison: Mask use vs. no mask: mean arterial pressure (93 ± 10 vs. 96 ± 10 mmHg, p = 0.025), HRV (high-frequency power: 54 vs. 40 msec, p = 0.005; high-frequency normalized power: 23.5 vs. 20.5 msec, p = 0.001; root mean square successive differences: 16.7 vs. 14.8 msec, p = 0.007)

Laumbach et al. (2014)	US, Piscataway, New Jersey	Not reported/ no reference given	Scripted Exposure	21, non-smoking healthy adults	Measurement: Mobile	PNC10-1000 nm	CPC 3007, TSI	Personal covariates and noise by design (cross-over and mixed model). In continuous per particle analysis, adjustment for pre-exposure level of outcome	EBC markers of inflammation; HRV	Standardized-clinical examinations	1.5 h ride in passenger vehicle	At immediately post-exposure, an IQR increase in PNC was associated with statistically significant increases in nitrite (99.4%, 32.1%; 166.7%) and nitrite + nitrate (75.7%, 21.5%; 130.0%) No significant associations between exposure to traffic particles and HRV outcomes at any of the time points. Continuous analysis: non-significant rises of EBC markers per IQR of PNC exposure
Kubesch et al. (2015)	Spain, Barcelona	022011-11/2011	Scripted exposure	28, healthy non-smoking adults 18-60 yrs	Measurement: Mobile	PNC10-1000 nm	CPC 3007	Sex, BMI, T, RH, ETS energy expenditure, NO2	BP	Standardized-clinical examinations	2h exposure	ß-estimates, IQRs not given in main text SBP post exposure 1.13 mmHg (0.28; 2.17) DBP post exposure: 0.89 mmHg (0.29; 1.50)

Mirabelli et al. (2015) Atlanta Commuter Exposure Study	USA, Atlanta	12/2009-06/2011	Scripted exposure	39, Non-smoking adults, meadian age: 32 yrs, 19 asthmatic and 21 non-asthmatic	Measurement: Mobile	Total	CPC model 3007	NA	Exhaled NO, Malondiadelhyde, FEV1 predicted, FVC % predicted, and FEF25–75 % predicted	Standardized-clinical examinations	2h commute by car	Percent changes, 0h, 1h, 2h, 3h post commute Exhaled NO: Non-asthmatics: 2 (-0.2; 0.6), 3 (-1.5; 9), 4 (-1; 10), -1 (-8; 5) Controlled asthmatics: -3.5 (-20; 10), -17 (-28; -3), -17 (-27; -0.5), -17 (-34; 4). Non-controlled asthmatics: 0 (-8; 11), -2 (-13; 9), 3 (-6; 17), 11 (-3; 28) FEV1, categories as above, Non-asthmatics: 1 (-0.2; 3), 1 (-0.2; 3), 1 (-0.5; 1.5), 1.5 (-1.5; 2.5) Controlled asthmatics: -2 (-6; 1.5), -1.5 (-5; 2), -1.5 (-6; 2.5), -1 (-8; 5.5) Non-controlled asthmatics: -1.5 (-3; 1), -1.5 (-3; 1), -1.5 (-4; 1), -3 (-8; 2)

Park et al. (2017)	USA, Sacramento (California)	03/2008 - 06/2008	Scripted exposure	32, healthy adults, frequent bicyclists, mean age 45.1	Measurement: Mobile	PNC >10	CPC,model 3007	Sex, age, wind direction, DoW	FVC, FEV1, FEV1/FVC, PEF	Standardized-clinical examinations	Bicycle ride (22km)	Change in ß-estimates per 12,225 to 36,833/ml FVC: -0.20 (-0.31; -0.08); FEV1: -0.15 (-0.22; -0.08) FEV1/FVC: 0.00 (-0.01; 0.01), PEF (liters/min): -3.10 (-15.39; 9.18)
Shutt et al. (2017)	Canada, Sault Ste. Marie Ontario	Not reported/ no reference given	Scripted Exposure	60, non-smoking adults, 18–55 yrs	Measurement: Central site	PNC10-1000	TSI model 3007	HR, age, sex, BMI, T, RH, study site	HRV and components	Standardized-clinical examinations	8h on site stay	Change in ß-estimates per 12,236/ml Heart rate (bpm): 1.10 (0.04; 2.16) HF power(ms²): -1.89 (-4.38; 0.60) LF power(ms²): -1.61 (-3.21; -0.01) HF/LF: -0.15 (-0.38; 0.08), SDNN (ms): -7.13* (-12.27; -1.98), RMSSD: -5.03 (-10.63; 0.57), pNN50: -2.20 (-4.24; -0.15)

Steen-hof et al. (2013) RAPTES study	The Neth-er-lands, Utrech t	03/2009-11/2009	Scripted Expo-sure	31, healthy non-smok-ing stu-dents	Measure-ment: Mobile	Total	CPC	T, RH, season	Cyto-kine IL-6 and IL-8, pro-tein and lac-toferr-in in nasal lav-age,IL-6 in blood	Standard-ized-clini-cal exami-nations	5h- AP meas-urement	Change in ß-esti-mates per 32,906/ml pre/ 2 h after ex-posure: NAL IL-6: -2.2 (p> 0.05) NAL protein: 7.9 (p> 0.05), NAL lactoferrin: 4.3 (p> 0.05), serum IL-6: 6.3 (p> 0.05)

Steen-hof et al. (2014) RAPTES study	The Neth-er-lands, Utrech t	03/2009-11/2009	Scripted Expo-sure	31, healthy non-smok-ing stu-dents	Measure-ment: Mobile	PNC7-3000nm	CPC	T, RH, season	WBC counts : Neu-tro-phils, Mono-cytes, Lym-pho-cytes, Eosin-ophile	Standard-ized-clini-cal exami-nations	5h- AP meas-ure-ment,	Percent changes per 28,100/ml Total WBC, 2h post expo: -2.2 (-5.3; 1.0), 18h post expo: -1.4 (-4.8; 2.2); Neutrophils 2h post expo: -1.3 (-6.2; 3.9), Monocytes 18h post expo: 3.4 (-1.0; 7.9) No robust associa-tion between PNC and the number of lymphocytes. No robust associa-tion between PNC and the number of eosinophils,

Strak et al. (2012) RAPTES study	The Netherlands, Utrecht	03/2009-11/2009	Scripted Exposure	31, healthy non-smoking students	Measurement: Mobile	NR	CPC	T, RH, season, low/high grasses and birch pollen counts, respir. infection	FVC, FEV1, FEF25–75%, PEF, FeNO, respire. symptoms	Standardized-clinical examinations	5h- AP measurement	Percent changes per 32,906/ml FeNO (immediately after exposure): 11.24 (5; 17) ($p < 0.05$), 2h postexpo: 12 (6; 17) next morning: 7 (0.5; 14%) FVC (immediately after exposure): –1.19 ($p < 0.05$),
Strak et al. (2013a) RAPTES study	The Netherlands, Utrecht	03/2009-11/2009	Scripted Exposure	31, healthy non-smoking students	Measurement: Mobile	PNC7-3000nm	CPC	Temperature, relative humidity, season, use of oral contraceptives	hs-CRP, fibrinogen, platelet counts, vWF, tPA/PAI-1	Standardized-clinical examinations	5h- AP measurement	Percent changes per 32,906/ml 25h post vs. pre: Hs-CRP: -4.31 (-14.35; 6.92) Platelet counts: -1.15 (-2.69; 0.40), vWF: -0.04 (-2.80; 2.80). Exposure of participants to PNC during transport was not associated with changes in acute vascular markers investigated.

Strak et al. (2013b) RAPTES study	The Neth-er-lands, Utrech t	03/2009-11/2009	Scripted Expo-sure	31, healthy non-smok-ing stu-dents	Measure-ment: Mobile	Total	CPC	Use of oral con-tracep-tives, T, RH, sea-son	Throm bin gener-ation	Standard-ized-clini-cal exami-nations	5h- AP meas-urement	Percent changes per 32,906/ml endogenous thrombin poten-tial in FXII-medi-ated thrombin generation path-way: Percent changes per 32,906/ml: all sites: (t=9–t=0): 5.83 (-39.62; 51.29), outdoor sites (t=9–t=0): -0.70 (-52.00; 50.60) all sites (t=25–t=0): -72.40 (-128.56; -16.24), outdoor sites (t=25–t=0): -66.59 (-124.78; -8.40) (post-pre) in ETP two hours after exposure in FXII-mediated throm-bin generation pathway,

Weichenthal et al. (2014)	Canada, Montreal	Summer 2013	Scripted Exposure	53, healthy non-smoking women 18-45 yrs, not taking AHM not pregnant or breastfeeding	Measurement: Mobile	PNC 10-100nm	Harvard Impactor and TSI Model 3007	Heart rate, T, caffeine, alcohol, race, age, BMI, recent illness, SHS	HRV (SDNN, RMSSD, pNN50, HF, LF, LF/HF), SBP, DBP, RHI	Standardized-clinical examinations	ma3h	Percent changes per 10,850/ml, lag 3h: RHI: ma 3h:-4.63 (-8.57; -0.693) SBP: 0.372 (-0.816; 1.56) DBP: 1.29 (-0.329; 2.91) SDNN, ma 3h: 3.61 (0.227; 7.00) numbers from suppl?) Abstract: in UFP exposure was associated with a 4.91% (95% CI: -9.31; -0.512) decrease RHI

[a] AccMP: Accumulation mode particles, AI: Augmentation index, AP: Augmentation pressure, AHM: Antihypertensive medications, AMP: Acuumulation mode particle , BAD: Baseline brachial artery diameter, BC: Black carbon, BDNF: Brain derieved neurotropic factor, BMI: Body mass index, CAD: Coronary artery disease, CD40L: Cluster of differentiation 40 ligand, CD62P: P-selectin (protein), CHF: Chronic heart failure, COPD: Chronic obstructive pulmonary disease, CRP: C-reactive protein, DBP: Diastolic blood pressure, DC: Deceleration capacity, DMA: Differential mobility analyzer, DMPS: Differential mobility particle sizer, DoW: Days of week, EBC: Exhaled breath condensate, eNO: Exhaled nitric oxide, ETS: Enviromental tobacco smoke, FEF 25 - 75: Forced expiratory flow at 25-75% of vital capacity, FeNO: Fractional exhaled nitric oxide , FEV1: Forced expiratory volume in 1 second, FVC: Forced vital capacity, FMPS: Fast mobility particle sizer spectrom, genet. susc.: Genetic susceptibility, HBA1c: Prediabetic marker, HDL: High density lipoprotein, HF: High frequency, HR: Heart rate, HR BP: Heart rate, blood pressure, HRT: Heart rate turbulence, HRV: Heart rate variability, hs-CRP: High-sensitive C-reactive protein, HTM: Hypertensive medication, ICD: International Classification of disease, IHD: Ischaemic heart disease, IGT: Impaired glucose tolerance, IL: Interleukin, LDL: Low density lipoprotein, LF: Low frequency, MA: Mean average, MAC: Mystic Activity Center, MDA: Malondialdehyde, MeanNN: Mean of normal-to-normal intervals , MI: Myocardial infarction, MVF: Microvascular function, MPO: Myeloperoxidase, NAL: Nasal lavage, NAL IL-6: , NR: No reference, OR: Odds ratio, OS: Oxidative stress, oxLDL: Plasma oxidized low-density lipoprotein, PEF: Peak expiratory flow, PEFR: Peak expiratory flow rates, PM: Particulate matter, PNC: Particulate number concentration, PNCacc: PNC accumulation mode particles, PNCait: PNC Aitken mode particles, PNCnuc: PNC nucleation mode particles, PNC::RR: PNC relative risk, PP: Pulse pressure, QT: Q wave and T wave interval, QTc: Heart rate corrected QT-interval, rCAVI: Right cardio-ankle vascular index, RH: Relative humidity, RHI: Reactive hyperemia index, RMSSD: Root mean square of the sucessive differences in ms., SES: Socio-economic status, SBP: Systolic blood pressure, SDNN: Standard deviation of normal-to-normal intervals, SHS: Second hand smoke exposure, SPH site: Harvard school of publich health, T: Temperature, T2DM: Type 2 diabetes mellitus, TNF-alpha: Tumor necrosis factor alpha, TNF-RII: Tumor necrosis factor-a-receptor II, tPA/PAI-1: Tissue plasminogen activator and plasminogen activator inhibitor-1, TpTe: Time from peak to end of T-wave , UFP: Ultrafine particle, vWF: Von Willebrand Factor, WBC: White blood cell counts.

[b] CPC: Condensation particle counter, MOUDI: Micro-Orifice-Uniform-Deposit Impactor, P-TRAK: UFP counter, SMPS: Scanning Mobility Particle Sizer, SMPS+C: Scanning mobility particle sizer and counter, TDMPS: Twin Differential Mobility Particle Sizer.

[c] CAFEH: Community Assessment of Freeway Exposure and Health, HEAPS: Health Effects of Air Pollution in Antwerp Schools, KORA: Cooperative Health Research in the Region Augsburg, RAPTES: Risk of Airborne Particles: a Toxicological–Epidemiological hybrid Study, RUPIOH: Relationship between Ultrafine and fine Particulate matter in Indoor and Outdoor air and respiratory Health.

Table A2a: Primary research articles presenting methods and results of UFP/ quasi-UFP epidemiologic long-term Studies, Mortality

Reference	Country, City	Study period	Study Design	Sample Size, Main study population	Exposure Assessment	Size Fractions	Technical device	Covariate adjustment	Outcome	Outcome Assessment	Exposure time windows	UFP effect sizes (conficence intervals)
Cohort												
Ostro et al. (2015) California Teachers Study	USA, California	01/2001 - 07/2007	Cohort	101,884 current and former female teachers and administrators, > 30 yrs	CTM	PNC10-100	NR	Strata: Age and race, adjusted for smoking status, smoking pack-years, adult SHS exposure, BMI, marital status, alcohol consumption, physical activity, menopausal status and HT use combined, family history of heart disease, hypertension medication/aspirin use, and dietary fat, fiber, and caloric intake	All -cause mortality, CV mortality, IHD mortality, Pulmonary mortality	Administrative database	2000 - 2007	HRs per 0.969 µg/ml: All-cause mortality: 1.01 (0.98; 1.05), CV mortality: 1.03 (0.97; 1.08), IHD mortality: 1.10 (1.02; 1.18), Pulmonary mortality: 1.01 (0.93; 1.10)

[a] CTM: Chemical transport model, CV: Cardiovascular, HR: Heart rate, IHD: Ischaemic heart disease, NR: No reference.

Table A2b: Primary research articles presenting methods and results of UFP/ quasi-UFP epidemiologic long-term Studies, Morbidity

Reference	Country, City	Study period	Study Design	Sample Size, Main study population	Exposure Assessment	Size Fractions	Technical device	Covariate adjustment	Outcome	Outcome Assessment	Exposure time windows	UFP effect sizes (conficence intervals)
Cross-sectional												
Li et al. (2017)	USA, Somerville Malden, Boston, Dorchester (Massachusets)	2009-2012	Cross-sectional	704 adults, ≥ 40 yrs,	LUR: Spatio-temporal, Microscale personal exposure model	Total (>4)	CPC TSI Model 3775	A) Age, sex, race, smoking status, education, income, time of residence at current address, percieved stress, work status, marital status, sample type, physical activity B) Plus BMI in subgroup C) Plus diagnoses (sensi.anal)	IHD, stroke, CHF; Self-report or medication for DM and/or hypertension	Self-reported	12 months, assumed to be stable over 7-11 years	ORs, increments NR Stroke/ IHD: 1.35 (0.83; 2.22) Diabetes: 0.71 (0.46; 1.10) Hypertension: 1.14 (0.81; 1.62)
Laurent et al. (2014)	USA, California	01/2001-12/2008	Cross-sectional	960,945	CTM	$PM_{0.1}$	Not reported/ reference given	Maternal race/ethnicity, education, parity, trimester primary care beginning, infant's gender, maternal age, length of gestation and median income	Term low birth weight	Administrative database	2000-2006	ORs per 0,4271 µg/m³: 1.03 (1.02; 1.03)

Case-control

Laurent et al. (2016b)	USA, California	01/2001-12/2008	Case-cohort	363,160, 72,632 cases, 290,528 controls	CTM, LUR: Spatio-temporal	CTM: <100 ($PM_{0.1}$) CALINE4: PNC (unclear)	CTM: CPC Model 3786	Race/ethnicity and educational level, maternal age and median household income at Census block	Term low birth weight	Administrative database	2000-2006 (PM0.1)	ORs per 6,444/ml PNC: 1.001 (0.989; 1.014) Primary PM0.1, per 1.359 µg/m³: 0.996 (0.981; 1.011) Onroad gasoline PM0.1 per 0.083µg/m³: 1.051 (1.015; 1.089)
Laurent et al. (2016a)	USA, California	01/2001-12/2008	Case-control	1,105,970, 442,314 cases, 710,360 controls	CTM, LUR: Spatio-temporal	CTM: <100 ($PM_{0.1}$) CALINE4: unclear (UFP)	CTM: CPC Model 3786	Race/ethnicity, educational level, maternal age, median household income	Pre-term birth	Administrative database	2000-2008	ORs PM0.1 per 1.389µg/m³: 1.021 (1.015; 1.028) PNC per 6,480/ml: 0.995 (0.988; 1.000) (geocoded at tax parcel level): 1.028 (1.021; 1.036)

[a] BMI: Body mass index, CALINEA: California Line Source Dispersion Model Version 4, CHF: Chronic heart failure, CTM: Chemical transport model, DM: Diabetes mellitus, IHD: Ischaemic heart disease, LUR: Land use regression, NR: No reference, OR: Odds ratio, PM: Particulate matter, PNC: Particulate number concentration, UFP: Ultrafine particle.
[b] CPC: Condensation particle counter.

Table A2c: Primary research articles presenting methods and results of UFP/ quasi-UFP epidemiologic long-term Studies, Subclinical Outcomes

Reference	Country, City	Study period	Study Design	Sample Size, Main study population	Exposure Assessment	Size Fractions	Technical device	Covariate adjustment	Outcome	Outcome Assessment	Exposure time windows	UFP effect sizes (conficence intervals)
Cross-sectional analysis within cohort												
Aguilera et al. (2016) SAPALDIA study	Switzerland, Basel/ Geneva/ Lugano/ Wald	2001/02 - 2010/11	cross-sectional analysis within cohort	1,503 Adults, ≥ 50 yrs, participants of Sapaldia 2 & 3	LUR	PNC10-300	miniDISC	sex, age, sex–age interaction, educational level, smoking status at SAPALDIA2 (S2), smoking pack-years between S2 +SAPALDIA3 (S3), smoking pack-years between S2 and S3)2, BMI at S2, (BMI at S2)2, BMI at S3 and (BMI at S3)	CIMT	Standardized-clinical examinations	2011-2012	Percent change per 10.-90. percentil PNC: 2.06 (0.03; 4.10) LDSA: 2.32 (0.23; 4.48)
Cohort												

Sunyer et al. (2015) BREATHE	Spain, Barcelona	01/2012 - 03/2013	Cohort	2,715, children from schools in low vs. high polluted areas	Central measurement at schools plus LUR for exposure assessment at home.	PNC10-700	miniDISC	Age, sex, maternal education, residential neighborhood SES, AP exposure at home, school and individual, traffic around school	Working memory, Superior working memory, Inattentiveness	Standardized-clinical examinations	Two weekly measurement campaigns averaged as long-term AP expos	Difference in cognitive development/ß-estimates, per 6,110/ml increase at baseline and 12-mo change Working memory: Baseline: -6.5 (-14; 1.5) 12-mo change: -4.9 (-10; 0.22) Superior working memory: Baseline: -0.95 (-7.4; 5.6), 12-mo change: -5 (-9.1; -0.96) Inattentiveness: Baseline: 4.5 (-4.0; 13) 12-mo change: 3.9 (0.31; 7.6)
Repeated measure within Cohort study												

Viehmann et al. (2015)	Germany, Essen/ Mülheim/ Bochum	2000-2002 (BL), 2006-2008 (FU)	Repeated measure within Cohort study	3,275 with baseline data, 3213 with follow-up data	CTM	PNC5-2,200	NR	Sex, (BMI), education, smoking, temperature (1–5 days moving average), season, short-term air pollutant (1–3 days moving average), time trend and time point.	hs-CRP, Fibrinogen, WCC, Platelets	Standardized-clinical examinations	365 days	Percent change per 27,000/ml hs-CRP: 3.8 (-0.6; 8.4), Fibrinogen: 1.0 (0.0; 2.0), WCC: 1.0 (-0.1; 2.1), Platelets: 0.6 (-0.4; 1.7)
Cross-sectional												
Lane et al (2015) CAFEH	USA, Somerville/ Boston (Massachusets)	07/2009 - 09/2010	Cross-sectional	140 Adults, ≥ 40 yrs	LUR: Spatio-temporal, Microscale personal exposure model	Total	CPC TSI Model 3775	Age, sex, BMI, smoking status (or SES instead of smoking status)	hs-CRP, IL-6	Standardized-clinical examinations	Annual average	ß-estimates, increment unclear, Personal exposure model: Residential annual average+ work+ other+highway+Aircondition: LN hsCRP: 1.26 (-0.02; 2.75) LN IL-6: 0.65 (-0.26; 1.55)

Lane et al. (2016) CAFEH	USA, Boston (Massachussets)	07/2009 - 02/2012	Cross-sectional	408 Adults, ≥ 40 yrs	LUR: Spatio-temporal, Microscale personal exposure model	PNC4-3,000	CPC TSI Model 3775	a) Age, sex, continuous BMI, smoking status and education. B) Age, sex, continuous BMI, smoking status, education and race/ethnicity. C) Age, sex, BMI, smoking status, education and nativity.	hsCRP, IL-6, TNFRII, Fibrinogen	Standardized-clinical examinations	Annual average	Percent change per 10,000/ml (IQR) a) hsCRP: 9.8 (-8.3; 31.4), IL-6: 5.8 (-5.6; 18.5), TNFRII: 3.6 (-1.9; 9.4), Fibr.: -1.9 (-5.5; 1.6) b) hsCRP: 14.0 (-4.6; 36.2), IL-6: 8.9 (-2.6; 21.8), TNFRII: 5.1 (-0.4; 10.9), Fibr: -1.9 (-5.5; 1.6) c) ähnlich wie b) White non-Hispanic, a) hsCRP: 32.7 (3.7; 67.2), IL6: 22.6 (-0.2; 45.5), TNFRII: 16.8 (5.8; 27.7), Fibr. -0.02 (-0.7; 0.7), East-Asian: a) hsCRP: 6.1 (-18.3; 31.0), IL6: 2.6 (-12.2; 17.3), TNFRII: 0.1 (-1.2; 1.4), Fibr. -0.06 (-5.4; 4.2),

[a] AP: Augmentation pressure, BMI: Body mass index, CIMT: Carotid intima-media thickness, CTM: Chemical transport model, Fibr.: Fibrinogen, hs-CRP: High-sensitive C-reactive protein, IL: Interleukin, LDSA: Lung deposited surface area, LN: Natural log, LUR: Land use regression, PNC: Particulate number concentration, SES: Socio-economic status, TNFRII: Tumor necrosis factor-a-receptor II, WCC: white blood cell count.

[b] CPC: Condensation particle counter, minidisc: Miniature diffusion size classifiers.

[c] BREATHE: Brain Development and Air Pollution Ultrafine Particles in School Children, CAFEH: Community Assessment of Freeway Exposure and Health, SAPALDIA: Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults.

Table A3a: Short-term studies with adjustment for co-pollutants, mortality

Reference	Expo-sure time win-dow	Outcome	UFP effect w/o co-pollutant adjustment	PM10 adjusted UFP effect	PM2.5 adjusted UFP effect	NO2 adjusted UFP effect	
Lanzinger et al. (2016a)	ma2-5	CV mortality, ma 2-5	RRs/ PNC20-100 per 2750/ml ma 2-5: -0.5 (-5.3; 4.5)	-	RRs/ PNC20-100 Ma 2-5: 0.5 (-0.5; 2)	RRs/ PNC20-100 Ma: 2-5: -5 (-7; -0.5)	
	ma2-5	Resp. morta-lity, ma 2-5	RRs/ PNC20-100 per 2750/ml ma 2-5: 8.5 (-4.8; 23.7)	-	Ma 2-5: 7 (-10; 30)	Ma 2-5: 14 (2.5; 26)	
Leitte et al. (2012)	ma0-3 ma0-4 lag2	Resp. mortality	Percentage change/ PNC300–1000 per 840/ml ma 0-3: 8.9 (1.3;17) ma 0-4: 11.5 (3.0;20.7) PNC total per 14,000/ml lag 2: 9.3 (1.3;17.9)	PNC300–1,000 ma 0-3: 3 (-8; 15) ma 0-4: 8 (-5; 21) PNC total lag2: 10 (2; 19)		PNC300–1000 ma 0-3: 2 (-9; –13) ma0-4: 6 (-7; 18) PNC total lag2: 9 (1.4; 17.9)	SO2: PNC300–1000 ma 0-3: 4 (-5; 15) ma0-4:.7 (-4; 18) PNC total lag2: 9 (1; 17.7)
Meng et al. (2013)	ma01	All-natural-cause mortal-ity	Percent change, all periods, per 2,600/ml PNC250–280: 2.41 (1.23; 3.58) per 63/ml PNC650-1,000 0.12 (-0.22; 0.45)	PNC250–280 1.75 (0.26; 3.24) PNC650-1,000 –0.12 (–0.56; 0.32)	PNC250–280 2.18 (0.81; 3.55) PNC650-1,000 –0.06 (–0.40; 0.29)	PNC250–280 1.66 (0.14; 3.17) PNC650-1000: 0.15 (–0.54; 0.25)	SO2, PNC250–280 2.04 (0.53; 3.54) PNC650-1,000 ma 0-1: –0.07 (–0.47; 0.33) PM2.5-10, PNC250-280: 2.52 (1.34 ; 3.71), PNC 650-1,000: 0.10 (–0.24; 0.44)

Samoli et al. (2016a)	lag1 lag1 lag2	non-accidental mortality CV mortality respiratory mortality	Percent changes per 5,180/ml -0.06 (-1.16; 1.06) -2.04 (-3.94; -0.10) -1.86 (-4.50; 0.86)				Effect estimates were generally robust to co-source adjustment, although mutual adjustment for all sources generally exerted greater influence on the estimates compared with estimates from two sources models.
Stafoggia et al. (2017)	lag5 lag6 lag7	Non-accidental mortality:	Percent increases PNC per 10,000/ml lag 5: 0.32 (-0.08; 0.72) lag 6: 0.35 (-0.05; 0.75) lag 7: 0.37 (-0.03; 0.7%)	Percent increases PNC per 10,000/ml lag 5: 0.16 (-0.25; 0.57) lag 6: 0.22 (-0.18; 0.63) lag 7: 0.28 (-0.13; 0.68)	Percent increases PNC per 10,000/ml lag 5: -0.14 (-0.80; 0.53) lag 6: -0.04 (-0.70; 0.62) lag 7: 0.01 (-0.74; 0.76)	Percent increases PNC per 10,000/ml lag 5: -0.08 (-0.55; 0.40) lag 6: -0.15 (-0.69; 0.38) lag 7: -0.25 (-0.72; 0.22)	PM2.5-10: similar to PM2.5 CO: lag 5: 0.22 (-0.25; 0.70) lag 6: 0.30 (-0.16; 0.77) lag 7: 0.13 (-0.35; 0.60) O3 lag 5: 0.40 (-0.02; 0.82) lag 6: 0.27 (-0.14; 0.69) lag 7: 0.30 (-0.12; 0.72)

Su et al. (2015)	ma05	overall CVD mortality	Percent increase per 8,328/ml PN3-100: ma 05: 8.8 (2.7; 15.2)	ma 05: 7.5 (3; 14)	ma 05: 7 (1; 13)	ma 05: 5 (-2; 12)	

[a] CO: Carbon monoxide, CV: Cardiovascular, CVD: Cardiovascular, MA: Mean average, NO2: Nitrogen dioxide, O3: Ozone, PM: Particulate matter, PNC: Particulate number concentration, RR: relative risk, SO2: Sulfur dioxide, UFP: Ultrafine particle.

Table A3b: Short-term studies with adjustment for co-pollutants, emergency/hospital visits/admissions

Reference	Exposure time win-dow	Outcome	UFP effect w/o co-pollutant adjustment	PM10 adjusted UFP effect	PM2.5 adjusted UFP effect	NO2 adjusted UFP effect	
Evans et al. (2014)	unclear	Number of pe-diatric asthma visits	ORs/PNC Lag 1: 0.89 (0.64; 1.24)per 3,007/ml Lag 4: 1.27 (0.9; 1.79) per 2,088/ml ORs/AccMP Lag 1: 0.73 (0.50;1.08) per 874/ml Lag 4: 1.00 (0.71;1.4) per 638/ml	Two-pollutant models using the pollutants shown to be associated with asthma exacerbation (ultrafine particles, carbon monoxide, and ozone). The effect esti-mates in these models did not differ substantially from those in the single-pol-lutant models (data not shown).			
Iskandar et al. (2012)	ma0-4	Hospital ad-missions due to asthma	ORs per 3,812.86/ml: 1.06 (0.98-1.14)	0.99 (0.92; 1.08)	0.99 (0.91; 1.08)	0.97 (0.89; 1.06)	NOx: 1 (0.91; 1.08)
Lanzinger et al. (2016b)	ma2-5	CV hospital ad-missions	RRs/ UFP per 2,750/ml ma 2-5: 0.3 (-1.7; 2.4)		-0.5 (-2; 1.5)	-0.7 (-2.1; 1)	
	ma0-5	Resp. hospital admissions	RRs/ UFP per 2,750/ml ma 0-5: 3.4 (-3.2; 7.3)		-3 (-11; 5)	-4 (-85; 2)	

Rosenthal et al. (2013)	lag0 lag2 lag0	Out-of hospital card. arrest, MI	ORs/ PNC per 10,624/ml: lag 0d: 1.27 (1.05; 1.54) lag 3d: 0.97 (0.80; 1.05) ORs/ AccMP per 1,007/ml lag 0d: 1.19 (1.04; 1.54) lag 2d: 0.96 (0.84; 1.10)		PNC lag 0d: 1.20 lag 3d: 0.99 AccMP lag 0d: 1.02 lag 2d: 0.93 p > 0.05		O3, PNC: lag 0d: 0.89 lag 3d: 1.10 AccMP lag 0d: 1.00 lag 2d: 0.98 p > 0.05
Samoli et al. (2016a)	lag1 lag2	CV hospital admissions, 15-65y 65y+ Respiratory hospital admissions, 0-14y 15-64y 65y+	Percent changes per 5,180/ml PNC 0.81 (-0.78; 2.42) -0.07 (-1.27; 1.15) 1.86 (-0.28; 4.05) -1.14 (-2.66; 0.41) -1.09 (-2.42; 0.27)				Adjustment of co-source estimates: Effect estimates of background urban NSD with either adult CVD or pediatric hospitalizations remained robust as did the estimates between nucleation PNC and pediatric hospital admissions.
Samoli et al. (2016b)	lags 0-7	Respiratory hospital admissions	Percentage changes per 10,000/ml lag 0: -0.44 (-1.73; 0.87) lag 1: -0.58 (-1.93; 0.79) lag 2: -0.22 (-0.92; 0.38) lag 5: 0.43 (-0.58; 1.45) lag 7: -0.37 (-1.39; 0.66)	lag 0: -0.73 (-2.21; 0.77) lag 1: -1.09 (-2.50; 0.34) lag 2: -0.58 (-1.24; 0.08) lag 5: 0.26 (-0.82; 1.36)	lag 0: -0.51 (-2.12; 1.14) lag 1: -0.70 (-2.39; 1.02) lag 2: -0.65 (-1.77; 0.49) lag 5: 0.33 (-1.17; 1.84)	lag 0: -0.42 (-2.08; 1.28) lag 1: -0.55 (-2.16; 1.09) lag 2: 0.04 (-0.67; 0.75) lag 5: -0.82 (-1.57; -0.07)	O3: lag 0: -0.05 (-1.14; 1.34) lag 1: 0.08 (-1.61; 1.80) lag 2: -0.14 (-0.76; 0.49) lag 5: 0.35 (-0.35; 1.29)

				lag 7: -0.24 (-1.36; 0.89)	lag 7: -0.68 (-1.96; 0.62)	lag 7: -0.83 (-2.09; 0.45)	lag 7: -0.30 (-1.27; 0.69)

[a] AccMP: Accumulation mode particles, CVD: Cardiovascular, NO2: Nitrogen dioxide, NOx: Nitrogen oxides, NSD: Size distributions of ultrafine particles, O3: Ozone, OR: Odds ratio, PM: Particulate matter, RR: Relative risk, UFP: Ultrafine particle.

Table A3c: Short-term studies with adjustment for co-pollutants, subclinical outcomes

Reference	Exposure time window	Outcome	UFP effect w/o co-pollutant adjustment	PM10 adjusted UFP effect	PM2.5 adjusted UFP effect	NO2 adjusted UFP effect	adjusted for different pollutants
Croft et al. (2017)	48h	Fibrinogen	UFP, percent changes, 1.90 (0.86; 2.95) per 1743/ml	-	2.46 (0.96; 3.96)	-	Delta-C: 2.76 (1.09; 4.42) BC: 2.50 (0.84; 4.16)
	12h	MPO	AccMP, per 452/ml, percent changes -2.80 (-4.68; -0.92)	-	-2.2 (-4.78;0.38)	-	Delta-C: -2.37(-5.18; 0.45) BC: -1.83(-4.44; 0.79)
	96h	MPO	UFP, per 1,434/ml, percent changes -5.55 (-8.51; -2.59)		-6.11 (-10.02; -2.20)		Delta-C: -5.77 (-9.99; -1.55) BC: -9.54 (-14.12; -4.95)
Gong et al. (2014)	depending on outcome	FeNO, EBC pH, EBC nitrite, WBC, urinary MDA, 8-OHdG	percentage changes FeNO, lag 0: 25.34 (12.96; 39.09) EBC pH, lag 1: 1.54 (0.79; 2.28) EBC nitrite, lag 6: 25.64 (16.12; 35.94), WBC, lag 0: 3.5 (1,7) urinary MDA,lag 3: 10.89 (0.56; 22.28 8-OHdG, lag 3: 28.56 (4.08; 59.53			FeNO: 26 (13; 40) EBC pH: similar EBC nitrite: 3 (-2; 18) WBC: similar urinary MDA, lag 3: 6.5 (-4; 17) urine 8-OHdG: 19 (-7; 44)	SO2 (further adjustments: see article) FeNO: 20 (6; 34) EBC pH: slightly lower EBC nitrite: 10 (0; 20) WBC: similar urinary MDA: 8 (-3; 19) urine 8-OHdG: 24 (0; 49)

Han et al. (2016)	ma 8h	FeNO	Percent changes, per 5.673/ml PNCait 11.68 (4.90; 18.89)		19 (9; 29)	17 (5; 28)	BC: 15 (7; 24) SO_2: 11 (1;20)
Janssen et al. (2015)	2h after exposure	FeNO	Percent change per 23,000/ml PNC, outdoor sites: 12.7 (6.0; 21.0)		13.0 (5; 19)	15.9 (6; 27)	O_3: 17.3 (8; 27)
	2h after exposure	IL-6 (nasal)	Percent change per 23,000/ml PNC, outdoor sites: 14.1 (-11; 50) When the underground site was included in the analysis, FeNO and NAL IL-6 were consistently associated with PNC		11.4 (-13; 45)	-5.7 (-31; 30)	O_3: 2.1 (-24,38)
	2h after exposure	FEV1	Percent change per 23,000/ml PNC, outdoor sites: -1.5 ($p < 0.05$)	-1.6 ($p < 0.05$)	-1.5 ($p < 0.05$)	-0.4	
Li et al. (2016)	lag1	FEF 50%	ß-estimates per 5,646.4/ml UFP: 0.40 (0.24; 0.56)				O_3: 0.25 (0.01; 0.48)
	lag1	FEF 75%	UFP: 0.29 (0.19; 0.39)				O_3: 0.16 (0.01; 0.30)
	lag1	FVC	UFP: 0.08 (-0.01; 0.18) AccMP: 0.00 (-0.10; 0.09)				O_3: 0.14 (0.00; 0.28) O_3: -0.04 (-0.17; 0.09)
	lag1	FEV1	UFP: 0.11 (0.02; 0.20) AccMP: 0.03 (-0.06; 0.12)				O3: 0.13 (-0.01; 0.26) O3: -0.03 (-0.15; 0.10)
Peters et al. (2015)	various	HR SDNN RMSSD	Percent changes per 16,000/ml personal PNC: SDNN, concurrent -0.56 (-1.02; -0.09), HR, lag 0-4 min: 0.23 (0.11; 0.36) lag 5-0 min: 0.16 (0.04; 0.28) RMSSD: estimates close to 0		lag unclear: estimates remain nearly the same		

Pieters et al. (2015)	lag0	SBP	ß-estimates (mmHg): PN20-30nm: 6.35 (1.56; 11.47) per 860/cm3 30–50 nm: 1.18 (0.05; 2.31), per 712/ml, 50–70 nm, 0.92 (–0.05; 1.89) per 540/ml, 70–100 nm: 0.86 (0.05; 1.68) per 358/ml, Total UFP: 2.92 (0.30; 5.61) per 1,666/ml		Similar results (see figure 3)		
Rich et al. (2012)	24-47h	TpTe (msec):	ß-estimates, per 2,680 particles/ml UFP: 0.33 (-0.32; 0.98) per 897/ml AccMP: 1.05 (0.28; 1.82) per 897/ml		(AccMP) 1.28 (0.25; 2.31)		AccMP: -0.26 (-1.06; 0.53) UFP: 1.23 (0.29; 2.17)
	0-5h	rMSSD (ms)	ß-estimates, per 2,680 particles/ml UFP: -3.19: (–5.32; –1.05) per 897/ml AccMP: -1.91 (-4.31; 0.49)				AccMP: -3.63 (-6.47; -0.79) UFP: -0.76 (-2.42; 3.94)
	72-95h	HRT (ms/RR)	ß-estimates, per 2,680 particles/ml UFP: 0.06 (-0.43; 0.55) per 897/ml AccMP: -0.67 (-1.18; -0.15)		(AccMP) -0.65 (-1.39; 0.07)		AccMP: 0.62 (0.04; 1.21) UFP: -1.05 (-1.68; -0.42)
	0-5h	SBP (mmHg)	ß-estimates, per 897/ml AccMP 0.63 (-0.27; 1.53)		(AccMP) 0.32 (-0.94; 1.57)		

	24-47h	Fibrinogen (g/L)	ß-estimates, per 2,680 particles/ml UFP: 0.08 (0.02; 0.14) per 897/ml AccMP: 0.12 (0.04; 0.20)		(AccMP) 0.12 (0.01; 0.23)		AccMP: 0.034 (-0.05; 0.11) UFP: 0.10 (-0.003; 0.19)
Rückerl et al. (2014)	ma05	CRP	percent change per 5,722/ml PNC (3-100) 12 (2; 23):		3 (-8; 17)		
Rückerl et al. (2016)	ma05	hsCRP	Percent change per 22.3 mm2/cm³ SC(DCPS) ma 5: 29.8 [15.9;45.3] per 168.9 mm²/cm³ SC10-800, ma 5: 9.2 (0.8; 18.3) per 0.06 SC3-10nm, ma 5: 9.6 (1.9; 18.0) per 5.7 SC30-50nm, ma 5, 3.2 (-3.9; 10.9) per 24.7 SC50-100nm, ma 5, 4.2 (-2.5; 11.4),	similar results, slightly weaker with SC(DCPS)			only adjusted for RHO2.5: apparent particle density of particulate matter with aerodynamic diameter <2.5µm and <10µm, respectively
	ma05	MPO, IL-6, fibrinogen.		MPO and IL-6 associations similar. Few associations slightly stronger, e.g. IL-6 with LC(EAD) and SC(DCPS), , some slightly weaker. For fibrinogen, associations were somewhat inconclu-sive for lag4: associations for both, LC (EAD) and SC(DCPS) turned from positive to negative, when adjusted for $PM_{2.5}$ or PM_{10}.			
Steenhof et al. (2013)	pre/ 2 h after exposure	NAL IL-6	Changes in ß-estimates per 32,906/ml all sites: -2.2 (p > 0.05)	-3.6 (p > 0.05)	-3.6 (p > 0.05)	-13.3 (p > 0.05)	
		NAL protein	7.9 (p > 0.05)	7.6 (p > 0.05)	7.8 (p > 0.05)	-1.3 (p > 0.05)	
		NAL lactoferrin	4.3 (p > 0.05),	-0.8 (p > 0.05)	1.2 (p > 0.05)	0.6 (p > 0.05)	
		serum IL-6	6.3 (p > 0.05)	7.2 (p > 0.05)	6.8 (p > 0.05)	5.8 (p > 0.05)	

Steenhof et al. (2014)	2h & 18h after exposure	total WBC	Percent changes per 28,100/ml 2h: -2.2 (-5.3; 1.0), 18h after expo: -1.4 (-4.8; 2.2)	-2.71 (p < 0.1) -2.00 (p > 0.05)	-2.50 (p > 0.05) -1.70 (p > 0.05)	-2.04 (p > 0.05) -1.08 (p > 0.05)	
	2h & 18h after exposure	Neutrophils	Percent changes per 28,100/ml 2h: -1.3 (-6.2; 3.9) 18h: -0.46	-1.97 (p > 0.05) -0.76 (p > 0.05)	-1.70 (p > 0.05) -0.57 (p > 0.05)	-2.01 (p > 0.05) -1.03 (p > 0.05)	
	2 h & 18 after exposure	Monocytes	2h: -0.31 (p > 0.05) 18h: 3.4 (-1.0; 7.9)	-0.44 (p > 0.05) 2.69 (p > 0.05)	-0.48 (p > 0.05) 3.04 (p > 0.05)	-0.13 (p > 0.05) 1.76 (p > 0.05)	
Strak et al. (2012)	immediately after exposure	FeNO	Percent changes per 32,906/ml 11.2 (p < 0.05)	11.3 (p < 0.05)	11.3 (p < 0.05)	14.7 (p < 0.05)	O3: 12.0 (p < 0.05)
	immediately after exposure	FVC	-1.19 (p < 0.05)	-1.26 (p < 0.05)	-1.26 (p < 0.05)	-0.60 (p > 0.05)	O3: -1.15 (p < 0.05)
Strak et al. (2013a)	25h post-pre	hs-CRP	Percent changes per 32,906/ml -4.31 (-14.35; 6.92)	-2.75 (-15.66; 5.32)	-5.23 (-15.15; 5.85)	-11.23* (-21.75; 0.71)	EC(fine): -9.91 (-20.56; 2.17) OC (coarse): -2.23 (-12.51; 9.26)
		Fibrinogen	-0.92 (-2.98; 1.19)	-1.12 (-3.19; 0.99)	-1.06 (-3.11; 1.05)	-1.40 (-3.77; 1.04)	
		Platelet counts	-1.15 (-2.69; 0.40),	-1.26 (-2.80; 0.32)	-1.21 (-2.75; 0.36)	-0.51 (-2.29; 1.30)	

		von-Willebrandt-Faktor:	-0.04 (-2.80; 2.80).	0.16 (-2.70; 3.09)	0.28 (-2.56; 3.20)	-0.73 (-3.88; 2.52)	
Strak et al. (2013b)	2h after exposure (t9-t0),	thrombin generation	Percent changes per 32,906/ml: all sites: (t9–t0): 5.83 (-39.62; 51.29), outdoor sites (t9–t0): -0.70 (-52.00; 50.60)	all sites: 3.17 (-43.10; 49.44) outdoor sites: -0.70 (-52.00, 50.60)	all sites: 3.40 (-42.14; 48.95) outdoor sites (t9–t0): 7.80 (-45.65; 61.25)	all sites: -27.76 (-79.32; 23.81) outdoor sites: 8.79 (-44.62; 62.20)	
	next morning (t25-t0)		all sites (t25–t0): -72.40 (-128.56, -16.24), outdoor sites (t25–t0): -66.59 (-124.78, -8.40)	all sites: -71.38 (-129.02, -13.73) outdoor: -80.02 (-139.74, -20.29)	all sites: -71.38 (-129.02; -13.73) outdoor: -79.46 ((-139.10; -19.82)	all sites: -47.39 (-114.60, 19.82) outdoor: -46.48 ((-112.47; 19.51)	
Sun et al. (2015)	ma04	SDNN	Percent changes PNC5-560: -7.9 (-9.7;-6.1) PNC10-20: -7 (-8.9;-5.1) PNC20-50: -6.6 (-8.1;-5) PNC50-100: -5.4 (-7.3;-3.4) PNC100-200: -3 (-4.6;-1.3) PNC200-560: -0.45 (-2.43;1.56).	-	-	PNC5-560: -7.73 (-9.57; -5.85) PNC 10-20: -7.21 (-9.14; -5.24) PNC20-50: -6.36 (-7.92; -4.77) PNC50-100: -5.65 (-7.69; -3.56) PNC100-200: -2.53 (-4.26; -0.77) PNC200-560: 0.09 (-1.96;2.18)	O_3: PNC5-560: -7.47 (-9.65; -5.24) PNC 10-20: -6.73 (-8.65; -4.77) PNC20-50: -6.07 (-7.77; -4.33) PNC50-100: -3.49 (-6.03;-0.89) PNC100-200: 0.3 (-1.84; 2.49) PNC200-560: 3.25 (0.97; 5.59)

Weichenthal et al. (2014)	lag3h	RHI	Percent changes per 10,850/ml: -4.91 (-9.31; -0.512)	+ adjustment for exposures during previous visits and regional air quality	-4.74 (-9.21; -0.26)	-5.03 (-9.52; -0.54)	-4.62 (-9.07; -0.168)
	lag3h	SBP	0.377 (-0.900; 1.65)		0.42 (-0.862; 1.70)	0.59 (-0.683; 1.86)	O_3: 0.57 (-0.70; 1.83)
	lag3h	DBP	1.61 (-0.155; 3.38)		1.65 (-0.115; 3.42	2.00 (0.253; 3.74)	O_3: 1.88 (0.126; 3.64)
	lag3h	SDNN	9.86 (0.245; 19.5)		3.74 (0.346; 7.14)	4.20 (0.855; 7.55)	O_3: 4.05 (0.721; 7.38)
Wu et al. (2012)		SDNN	$PM_{0.25}$,: -4.7 (-14.5; 6.2), rMSSD: -5.1 (-12.4; 3.0), HF: -5.7 (-16.5; 6.5), LF: -4.8 (-15.1; 6.8), LF/HF: 1.0 (-2.8; 5.0)	Appendix not available, author did not respond to email.			
Zhang et al. (2013)	lag3	HR	Percent changes per 6,572/ml 0.5 (0.1; 1.0)			0.7 (-0.2; 1.3)	O_3: 0.6 ((0.2; 1.2)
	lag3	HF	-5 (-1; -8)			(lag 1): -0.5 (-9; 1)	O_3 (lag4) -7 (-9; -3)

	lag3	CRP, fibrinogen, BCC & differentials, 8OHdG, FeNO, EBC pH, nitrate, nitrite, +nitrate, 8-isoprostane), CD62P sCD40L], platelet aggregation, vWF, BP				mostly similar	mostly similar
Zhang et al. (2016a)	ma5	FeNO	Percent changes, stronger estimated associations for ultrafine $PM_{0.18}$ than larger size-fractions for total mass $PM_{0.18}$: 3.0 (0.7; 5.3) per 1.1 µg/m³ AccMP: -0.8 (-3.5; 1.9) per 4.0 µg/m³ (various outcomes (elements and PAHs in $PM_{0.18}$) in figure 1&2 and supplementary tables) MDA: positively associated with total $PM_{0.18}$	The estimates of association from two-pollutant models of O3 with a primary air pollutant (BC, NO_x and PAHs) became largely nonsignificant with effect estimates attenuating toward the null for airway biomarkers, except for associations between FeNO and PAHs in $PM_{0.18}$ that remained significant. The results for the systemic biomarkers were similar using two-pollutant models and single-pollutant models (data not shown)			
Zhang et al. (2016b)	ma5	RHI	$PM_{0.18}$ per 1.13 µg/m3 -0.01 (-0.05; 0.03) (only figures)				O_3: 0.15 (0.04; 0.06)

[a] 8-OHdG: Urinary 8-hydroxy-2'-deoxyguanosine, AccMP: Accumulation mode particles, BC: Black carbon, BCC: Blood cell counts, BP: Blood pressure, CD62P: P-selectin (protein) sCD40L: soluble CD40 ligand, CRP: C-reactive protein, DBP: Diastolic blood pressure, Delta-C: Estimate of wood smoke pollution, EBC: Exhaled breath condensate pH, EC(fine): Elemental carbon, FeNO: Fractional exhaled nitric oxide, FEF 50-75: Forced expiratory flow at 50-75% of vital capacity, FEV1: Forced expiratory volume in 1 second, FVC: Forced vital capacity, HF: High frequency, HR: Heart rate, HRT: Heart rate turbulence, hs-CRP: High-sensitive C-reactive protein, IL: Interleukin, LC(EAD): Particle length concentration measured by Electric Aerosol Detector, MA: Mean average, MDA: Malondialdehyde, MPO: Myeloperoxidase, NAL: Nasal lavage, NO2: Nitrogen dioxide, NOx: Nitrogen oxides, O3: Ozone, OC(coarse), PAHs: Polycyclic aromatic hydrocarbons, PM: Particulate matter, PNCait:

PNC Aitken mode particles, RHI: Reactive hyperemia index, RMSSD: Root mean square of the sucessive differences in ms., SBP: systolic blood pressure, SC(DCPS): Particle surface concentration measured by Diffusion charging particle sensor, SDNN: Standard deviation of normal-to-normal intervals, SO2: Sulfur dioxide, TpTe: Time from peak to end of T-wave, UFP: Ultrafine particle, vWF: Von Willebrand Factor, WBC: White blood cell counts. Purple color: estimates originate from figures

Table A4a: Long-term studies with adjustment for co-pollutants, mortality

Reference	Exposure time winDoW	Outcome	UFP effect w/o co-pollutant adjustment	PM10 adjusted UFP effect	PM2.5 adjusted UFP effect	NO2 adjusted UFP effect	adjusted for different pollutants
Ostro et al. (2015)		IHD mortality	HRs per 0.969 µg/ml: 1.10 (1.02; 1.18),	We examined two-pollutant models for UF (SOA_ant) with each of the other UF constituents. For secondary organic aerosol - anthropogenic UFs, the HR was basically unchanged and only one other constituent, Cu, was also statistically significantly related to IHD mortality			

[a] CU: Copper, HR: Heart rate, IHD: Ischaemic heart disease, NO2: Nitrogen dioxide, PM: Particulate matter, UFP: Ultrafine particle.

Table A4b: Long-term studies with adjustment for co-pollutants, subclincal outcomes

Reference	Exposure time winDoW	Increment	UFP effect w/o co-pollutant adjustment	PM10 adjusted UFP effect	PM2.5 adjusted UFP effect	adjusted for different pollutants
Aguilera et al. (2016)	2011-2012	CIMT	Percent change per 10.-90. percentil PNC (main model): 2.06 (0.03; 4.10) LDSA (main model): 2.32 (0.23; 4.48)	2.13 (–2.31, 6.57)	0.63 (–3.60, 4.86)	LDSA: -1.11 (–8.00; 5.78) PNC: 3.41 (-3.65; 10.46)

[a] CIMT: Carotid intima-media thickness, LDSA: Lung deposited surface area, NO2: Nitrogen dioxide, PM: Particulate matter, UFP: Ultrafine particle.

Table A5a: Objective quality indicators, short-term studies, mortality

Reference	Study population specified	Sample type of study population	Response Rate [%]	Subjects recruited from same or similar populations	Subjects recruited from same time period	Sample representative for general population	Lost to follow-up after Baseline provided	Losses to follow-up likely to introduce bias	exposure assignment	Complete or partial residential address historyprovided	Description of size ranges	QA/QC for UFP measures described?	Exposure assessment implemented consistently across all study participants	Outcome measures clearly defined and implemented consistently	Outcome assessors blinded to exposure status resp. Case-control status of participants	Analysis adjusted for other air pollutants
Lanzinger et al. (2016)	Yes	NA	NA	No	No	CR	NA	NA	NA	NA	Yes	Yes	Yes	Yes	NA	Yes
Leitte et al. (2016)	Yes	NA	NA	Yes	Yes	CR	NA	NA	NA	NA	Yes	No	Yes	Yes	Yes	Yes
Meng et al. (2013)	Yes	NA	NA	Yes	Yes	CR	NA	NA	NA	NA	Yes	Yes	Yes	Yes	Yes	Yes
Samoli et al (2016a)	Yes	CS	NA	Yes	Yes	CR	NA	NA	NA	NA	Yes	No	Yes	Yes	Yes	Yes
Stafoggia et al. (2017)	Yes	NA	NA	Yes	No	CR	NA		City	NA	Yes	Yes	No	Yes	Yes	Yes

Su et al. (2015)	Yes	NA	NA	Yes	Yes	CR	NA	NA	NA	NA	Yes	No	Yes	Yes	Yes	Yes
Wolf et al. 2015	Yes	Other	NA	Yes	Yes	CR	NA	NA	NA	NA	Yes	No	No	Yes	Yes	No

CS: Convenience Sample, CR: Completely representative, NA: Not applicable,

Table A5b: Objective quality indicators, short-term studies, morbidity

Reference	Study population specified	Sample type of study population	Response Rate [%]	Subjects recruited from same or similar populations	Subjects recruited from same time period	Sample representative for general population	Lost to follow-up after Baseline provided	Losses to follow-up likely to introduce bias	Exposure assignment	Complete or partial residential address historyprovided a	Description of size ranges	QA/QC for UFP measures described?	Exposure assessment implemented consistently across all	Outcome measures clearly defined and implemented	Outcome assessors blinded to exposure status resp. Case-control status	Analysis adjusted for other air pollutants
Cole-Hunter et al. (2013)	Not specified/ RG	NR/NR	NA	Yes	Yes	SG	NA	NA	Mobile personal	NA	Yes	Yes	Yes	Yes	NR/ NR	No
Karakatsani (2012)	Yes	CS	NA	No	Yes	SG	NR/NR	Cannot det.	City	NA	Total	Yes	Yes	Yes	Yes	No
Langrish et al. (2012)	Yes	CS	NA	Yes	Yes	SG	NA	NA	Mobile personal	NA	No	No	Yes	Yes	NA	No
Link et al. (2013)	Yes	CS	NA	Yes	Yes	SG	Yes	Yes	NA	NA	No	No	Yes	Yes	Yes	No

Mehta et al. (2015)	Yes	Other	Sub-goup of larger co-hort	Yes	Yes	SG	Yes	Yes	City	NR/ RG	Yes	Yes	Yes	Yes	Yes	No
Wang et al. (2014)	Yes	RS	NR/ RG	Yes	No	SG	NR/ NR	CD	NA	NA	No	No	Yes	Yes	Yes	No
Wolf et al. 2015	Yes	Other	NA	Yes	Yes	CR	NA	NA	NA	NA	Yes	No	Yes	Yes	Yes	No

CD: Cannot determin , CS: Convenience Sample, CR: Completely representative, SR: Somewhat representative, SG: selected group, NA: Not applicable, NR/NR: Not reported/ no reference given, NR/RG: Not reported/ reference given

Table A5c: Objective quality indicators, short-term studies, emergency/hospital admissions

Reference	Study population specified	Sample type of study population	Response Rate [%]	Subjects recruited from same or similar populations	Subjects recruited from same time period	Sample representative for general population	Lost to follow-up after Baseline provided	Losses to follow-up likely to introduce bias	Exposure assignment	Complete or partial residential address historyprovided	Description of size ranges	QA/QC for UFP measures described?	Exposure assessment implemented consistently across all study participants	Outcome measures clearly defined and implemented consistently	Outcome assessors blinded to exposure status resp. Case-control status of participants	Analysis adjusted for other air pollutants
Delfino et al. (2014)	Yes	CS	NA	Yes	Yes	SR	NA	NA	Geo-coded addresses	No complete residential address history	NR/RG	No	Yes	Yes	Yes	No
Diaz-Robles et al. (2014)	NS/NR	CS	NA	Yes	Yes	SR	NA	NA	NA	NA	Yes	No	Yes	Yes	Yes	No
Evans et al. (2014)	Yes	CS	NA	Yes	Yes	SG	NR/NR	No	NA	NA	Yes	NR/NR	Yes	Yes	NA	Yes

Gardner et al. (2014)	Yes	NA	NA	Yes	Yes	SG	NA	NA	City	NA	Yes	Yes	Yes	Yes	Yes	No
Iskandar et al. (2012)	Yes	CS	NA	Yes	Yes	SR	NA	NA	NA	NA	Yes	NR/NR	Yes	Yes	NA	Yes
Lanzinger et al. (2016)	Yes	NA	NA	No	No	CR	NA	NA	NA	NA	Yes	Yes	Yes	Yes	NA	Yes
Liu et al. (2013)	Yes	NA	NA	Yes	Yes	CR	NA	NA	NA	NA	Yes	No	Yes	Yes	NA	No
Rosenthal et al. (2013)	Yes	NA	NA	Yes	Yes	SG	NA	NA	NA	NA	Yes	No	Yes	Yes	Yes	Yes
Samoli et al (2016a)	Yes	CS	NA	Yes	Yes	CR	NA	NA	NA	NA	Yes	No	Yes	Yes	Yes	Yes
Samoli et al. (2016b)	Yes	NA	NA	Yes	No	CR	NA	NA	NA	NA	Yes	Partly	No	Yes	Yes	Yes
Wichmann et al. (2013)	Yes	NA	NA	Yes	Yes	SG	NA	NA	NA	NA	Yes	No	Yes	Yes	NA	No

CR: Completely representative, CS: Convenience Sample, NA: Not applicable, NR/NR: Not reported/ no reference given, NR/RG: Not reported/ reference given, NS/NR: Not specified/ no reference given, SG: selected group, SR: Somewhat representative.

Table A5d: Objective quality indicators, short-term studies, subclinical outcomes

Reference	Study population specified	Sample type of study population	Response Rate [%]	Subjects recruited from same or similar populations	Subjects recruited from same time period	Sample representative for general population	Lost to follow-up after Baseline provided	Losses to follow-up likely to introduce bias	Exposure assignment	Complete or partial residential address historyprovided a	Description of size ranges	QA/QC for UFP measures described?	Exposure assessment implemented consistently across all participants	Outcome measures clearly defined and implemented	Outcome assessors blinded to exposure status resp. Case-control status of participants	Analysis adjusted for other air pollutants
Bartell et al. (2013)	Yes	CS	NA	Yes	Yes	SG	Yes	No	Micro-environments	NA	Yes	No	Yes	Yes	Yes	No
Bind et al. (2016)	Yes	CS	NA	Yes	Yes	SG	NR/ RG	Yes	NA	Yes	Yes	No	Yes	Yes	Yes	No
Bos et al. (2011)	Not specified/ RG	CS	NA	Yes	Yes	SG	NA	NA	Mobile personal	NA	No	No	Yes	Yes	No	No
Bos et al. (2013)	Yes	CS	NA	No	Yes	SG	NA	NA	NA	NA	Yes	No	Yes	Yes	No	No

Chung M. et al. (2015)	Yes	Random + CS	NR/ RG	Yes	Yes	SG	NR/ RG	CD	NA	NA	No	NR/ NR	Yes	Yes	Yes	No
Cole-Hunter et al. (2013)	Not specified/ RG	NR/NR	NA	Yes	Yes	SG	NA	NA	Mobile personal	NA	Yes	Yes	Yes	Yes	NR/ NR	No
Cole-Hunter et al. (2016)	Yes	NR/ NR	NR/ NR	Yes	Yes	SG	NR/ NR	NA	Mobile personal	NA	Yes	Yes	Yes	Yes	No	No
Croft et al. (2017)	Yes	CS	NA	Yes	Yes	SG	NA	NA	NA	NA	Yes	No	Yes	Yes	Yes	Yes
Frampton et al. (2012)	Yes	NR/ NR	NR/ NR	Yes	Yes	SG	Yes	No	City	NA	Yes	Yes	Yes	Yes	Yes	No
Fuller et al. (2015)	Yes	NR/ NR	NA	No	NR/ NR	SR	NA	NA	city, geo-coded adress	NR/ NR	No	No	Yes	Yes	NA	No
Gong et al. (2014)	Yes	NR/NR	NR/NR	Yes	Yes	SG	NR/RG	NA	City	No	Yes	Yes	Yes	Yes	Yes	Yes
Hampel et al. (2012)	Yes	NR/ NR	NA	Yes	Yes	SG	NA	Yes	City	NR/ NR	Yes	No	Yes	Yes	NA	No

Hampel et al. (2014)	Yes	NA	NA	Yes	NA	SG	NA	NA	Mobile personal	NA	Yes	No	Yes	Yes	NR/ NR	NR/ NR
Han et al. (2016)	Yes	CS	NA	Yes	Yes	SG	NR/ NR	CD	NA	NA	Yes.	Yes	Yes	Yes	Yes	Yes
Hoffmann et al. (2012)	Yes	CS	NA	Yes	Yes	SG	NR/ NR	No	NA	NA	No	No	Yes	Yes	Yes	No
Huttunen et al. (2012)	Yes	CS	84	Yes	Yes	SG	NR/ NR	No	NA	NA	Yes	No	Yes	Yes	Yes	No
Janssen et al. (2015)	Yes	CS	NA	Yes	Yes	SG	NA	NA	Micro-environments	NA	NO	Yes	Yes	Yes	Yes	Yes
Jarjour et al. (2013)	Yes	CS	NA	Yes	Yes	SG	NA	NA	Mobile personal	NA	Yes	Yes	Yes	Yes	No	No
Karottki et al (2015)	Yes	CS	NA	Yes	Yes	SG	Yes	No	Micro-environments, NA	NR/ NR	Yes	No	Yes	Yes	Yes	No

Karottki et al. (2014)	Yes	NA	NA	Yes	Yes	SG	NA	NA	Micro-environments	Yes, complete RH	Yes	Yes	Yes	Yes	Yes	No
Kubesch et al. (2015)	Yes	CS	NA	NR/ NR	Yes	SG	Yes	No	Micro-environments	NA	Yes	Yes	Yes	Yes	No	No
Langrish et al. (2012)	Yes	CS	NA	Yes	Yes	SG	NA	NA	Mobile personal	NA	No	No	Yes	Yes	NA	No
Laumbach et al. (2014)	Yes	CS	NA	Yes	Yes	SG	NR/ NR	CD	Mobile personal	Yes	Yes	No	Yes	Yes	NR/ NR	No
Li et al. (2016)	Yes	Random + CS	NR/ NR	Yes	Yes	SG	NR/ NR	CD	City	NA	Yes	No	Yes	Yes	Yes	Yes
Ljungman et al. (2014)	Yes	RS	NR/ NR	No	No	SR	NA	NA	NA	NA	No	No	Yes	Yes	Yes	No
Manney et al. (2012)	Yes	CS	NA	No	Yes	SG	NR/ NR	CD	Geo-coded addresses	NA	Yes	Yes	Yes	Yes	Yes	No

Mehta et al. (2014)	Yes	Other	Sub-goup of larger co-hort	Yes	Yes	SG	Yes	Yes	City	NR/ RG	Yes	Yes	Yes	Yes	Yes	No
Mira-belli et al. (2015)	Yes	CS	NA	Yes	Yes	SG	NA	NA	Mo-bile per-sonal	NA	No	Yes	Yes	Yes	No	No
Olsen et al. (2014)	Yes	Ran-dom + CS	20	Yes	Yes	SR	NA	NA	Mi-cro-envi-ron-ments , Mo-bile per-sonal	Yes	Yes	Yes	Yes	Yes	Yes	No
Park et al. (2017)	Yes	CS	NA	No	Yes	SG	NA	NA	Mo-bile per-sonal	NA	No	Yes	Yes	Yes	No	No
Peng et al. (2016)	Yes	CS	NA	Yes	Yes	SG	NR/ NR	No	NA	NA	No	No	Yes	Yes	Yes	No
Peters et al. (2015)	Yes	NR/ NR	NR/ NR	Yes	Yes	SG	NR/ NR	NA	NA	NA	Yes	Yes	Yes	Yes	NR/ NR	Yes

Pieters et al. (2015)	Yes	CS	NA	No	Yes	SG	Yes	No	Micro-environments	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Rich et al. (2012)	Yes	CS	NA	Yes	Yes	SG	NR/NR	NA	NA	NA	Yes	No	Yes	Yes	Yes	Yes
Rückerl et al. (2014)	Yes	Other	NA	Yes	Yes	SG	NR/NR	NA	NA	NA	Yes	No	Yes	Yes	Yes	Yes
Rückerl et al. (2016)	Yes	Other	NA	Yes	Yes	SG	NR/NR	NA	NA	NA	Yes	Yes	Yes	Yes	Yes	Yes
Sarnat et al. (2014)	Yes	CS	NA	Yes	Yes	SG	Yes	No	Mobile personal	NA	No	No	Yes	Yes	Yes	NR/NR
Shutt et al. (2017)	Yes	CS	NA	Yes	Yes	SR	NA	NA	NA	NA	Yes	No	Yes	Yes	No	No
Song et al. (2013a)	Yes	CS	NA	Yes	Yes	SG	Yes	No	Micro-environments	NA	Yes	No	Yes	Yes	Yes	No
Song et al. (2013b)	Yes	CS	NA	Yes	Yes	SG	NR/NR	NA	Micro-environments	NA	Yes	No	Yes	Yes	Yes	No

Steen-hof et al. (2013)	Yes	CS	NA	Yes	Yes	SG	NA	NA	Mi-cro-envi-ron-ments	NA	No	No	Yes	Yes	No	Yes
Steen-hof et al. (2014)	Yes	CS	NA	Yes	Yes	SG	NA	NA	Mi-cro-envi-ron-ments	NA	Yes	Yes	Yes	Yes	Yes	Yes
Strak et al. (2012)	Yes	CS	NA	Yes	Yes	SG	NA	NA	Mi-cro-envi-ron-ments	NA	No	No	Yes	Yes	No	Yes
Strak et al. (2013a)	Yes	CS	NA	Yes	Yes	SG	NA	NA	Mi-cro-envi-ron-ments	NA	Yes	No	Yes	Yes	No	Yes
Strak et al. (2013b)	Yes	CS	NA	Yes	Yes	SG	NA	NA	Mi-cro-envi-ron-ments	NA	No	No	Yes	Yes	No	Yes
Sun et al. (2015)	Yes	CS	NA	Yes	Yes	SG	NR/ NR	CD	NA	NA	Yes	No	Yes	Yes	Yes	Yes
Wang et al. (2016)	Yes	CS	NA	Yes	Yes	SG	NR/ NR	NA	NA	NA	Yes	No	Yes	Yes	Yes	No

Weichenthal et al. (2014)	Yes	CS	NA	Yes	Yes	SG	NA	NA	Mobile personal	NA	Yes	No	Yes	Yes	No	Yes
Wittkopp et al. (2013)	Yes	CS	NA	Yes	Yes	SG	NR/NR		Retirement community	NA	Yes	No	Yes	Yes	NA	No
Wu et al. (2012)	Yes	CS	NA	Yes	Yes	SG	NR/NR	NA	Mobile personal	NA	Yes	No	Yes	Yes	Yes	Yes
Zanobetti et al. 2014	Yes	CS	NA	Yes	Yes	SG	NR/NR	No	NA	NA	No	No	Yes	Yes	Yes	NR/NR
Zhang et al. (2013)	Yes	CS	NA	Yes	Yes	SG	Yes	No	NA	NA	Yes	Yes	Yes	Yes	Yes	Yes
Zhang et al. (2016a)	Yes	CS	NA	Yes	Yes	SG	NR/NR	CD	Mobile personal	NA	Yes	Yes	Yes	Yes	Yes	Yes
Zhang et al. (2016b)	Yes	CS	NA	NR/NR	Yes	SG	NR/NR	CD	NA	NA	Yes	Yes	Yes	Yes	Yes	Yes

CD: Cannot determine, CR: Completely representative, CS: Convenience Sample, NA: Not applicable, NR/NR: Not reported/ no reference given, NR/RG: Not reported/ reference given, SG: selected group, SR: Somewhat representative.

Table A6a: Objective quality indicators, long-term studies, mortality

Reference	Study population specified	Sample type of study population	Response Rate [%]	Subjects recruited from same or similar populations	Subjects recruited from same time period	Sample representative for general population	Lost to follow-up after Baseline provided	Losses to follow-up likely to introduce bias	Exposure assignment	Complete or partial residential address historyprovided a	Description of size ranges	QA/QC for UFP measures described?	Exposure assessment implemented consistently across all	Outcome measures clearly defined and implemented	Outcome assessors blinded to exposure status resp. Case-control status of participants	Analysis adjusted for other air pollutants
Ostro et al. (2015)	Yes	RS	40	Yes	Yes	SG	Yes	CD	Micro-environments	Yes	Yes	Yes	Yes	Yes	Yes	Yes

CD: Cannot determine, RS: Random sample, SG: selected group.

Table A6b: Objective quality indicators, long-term studies, morbidiy

Reference	Study population specified	Sample type of study population	Response Rate [%]	Subjects recruited from same or similar populations	Subjects recruited from same time period	Sample representative for general population	Lost to follow-up after Baseline provided	Losses to follow-up likely to introduce bias	Exposure assignment	Complete or partial residential address historyprovided a	Description of size ranges	QA/QC for UFP measures described?	Exposure assessment implemented consistently across all	Outcome measures clearly defined and implemented	Outcome assessors blinded to exposure status resp. Case-control status of participants	Analysis adjusted for other air pollutants
Laurent et al. (2014)	Yes	Other	NA	Yes	Yes	SG	NA	NA	Geo-coded addresses	NR/ NR	Yes	Yes	Yes	Yes	Yes	No
Laurent et al. (2016a)	Yes	Other	NA	Yes	Yes	SG	NA	NA	Geo-coded addresses	NR/ NR	Partly	Yes	Yes	Yes	Yes	No
Laurent et al. (2016b)	Yes	Other	NA	Yes	Yes	SG	NA	NA	Geo-coded addresses	NR/ NR	Partly	No	Yes	Yes	Yes	No

Li et al. (2017)	Yes	Random + CS	NR/ NR	No	Yes	SR	NA	NA	Micro-environments	Yes	Yes	No	Yes	Yes	Yes	No

CS: Convenience Sample, NA: Not applicable, NR/NR: Not reported/ no reference given, SG: selected group, SR: Somewhat representative.

Table A6d: Objective quality indicators, long-term studies, subclinical outcomes

Reference	Study population specified	Sample type of study population	Response Rate [%]	Subjects recruited from same or similar populations	Subjects recruited from same time period	Sample representative for general population	Lost to follow-up after Baseline provided	Losses to follow-up likely to introduce bias	Exposure assignment	Complete or partial residential address historyprovided a	Description of size ranges	QA/QC for UFP measures described?	Exposure assessment implemented consistently across all	Outcome measures clearly defined and implemented	Outcome assessors blinded to exposure status resp. Case-control status of participants	Analysis adjusted for other air pollutants
Aguilera et al. (2016)	Yes	RS	NR/ RG	Yes	Yes	SR	NR/ RG	Yes	Micro-environments	Yes	Yes	No	Yes	Yes	Yes	Yes
Lane et al (2015)	Yes	RS + CS	NR/ NR	No	Yes	SR	NA	NA	Micro-environments	NR/ NR	No	Yes	Yes	Yes	Yes	No

Lane et al. (2016)	Yes	RS + CS	NR/ RG	No	No	SR	NA	NA	Micro-environ-ments	NR/ NR	Yes	Yes	Yes	NR/ RG	Yes	No
Sunyer et al. (2015)	Yes	RS	59	Yes	Yes	SR	Yes	No	NA	No	Yes	No	Yes	Yes	No	No
Viehmann et al. (2015)	Yes	RS	NR/ NR	Yes	Yes	SR	NR/ RG	Can-not de-ter-mine	Geo-coded ad-dresses	Yes	Yes	No	Yes	Yes	Yes	No

CS: Convenience Sample, NA: Not applicable, NR/NR: Not reported/ no reference given, NR/RG: Not reported/ reference given, RS: Random sample, SG: selected group, SR: Somewhat representative.