International Journal of Public Health (2019) 64:547–559
https://doi.org/10.1007/s00038-019-01202-7

REVIEW

Health effects of ultrafine particles: a systematic literature review update of epidemiological evidence

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Received: 10 August 2018 / Revised: 4 January 2019 / Accepted: 9 January 2019 / Published online: 21 February 2019

Abstract

Objectives Due to their small size, ultrafine particles (UFP) are believed to exert higher toxicity than larger particles. As numerous studies on health effects of UFP have been published since the last systematic review in 2013, we aim to systematically review the new literature.

Methods We searched MEDLINE and the specialized LUDOK database for studies published between 01.01.2011 and 11.05.2017 investigating health effects of ambient air pollution-related UFP. We included epidemiologic studies containing UFP measures and quantifiable measures of associations. Relevant data were extracted on the basis of previously developed evaluation criteria.

Results We identified 85 original studies, conducting short-term (n = 75) and long-term (n = 10) investigations. Panel (n = 32), scripted exposure with predefined settings (n = 16) or time series studies (n = 11) were most frequent. Thirty-four studies adjusted for at least one other pollutant. Most consistent associations were identified for short-term effects on pulmonary/systemic inflammation, heart rate variability and blood pressure.

Conclusions The evidence suggests adverse short-term associations with inflammatory and cardiovascular changes, which may be at least partly independent of other pollutants. For the other studied health outcomes, the evidence on independent health effects of UFP remains inconclusive or insufficient.

Keywords Ultrafine particles · Air pollution · Epidemiology · Health effects · Particulate matter

Introduction

Ambient particulate matter (PM) air pollution increases all-cause mortality and has negative health impacts particularly on respiratory, cardiometabolic and cognitive health, and early childhood development (Thurston et al. 2017). It was estimated that ambient air pollution (AAP) is the most important environmental risk factor for mortality worldwide (Cohen et al. 2017; Forouzanfar et al. 2016). At the EU level, AAP is estimated to reduce life expectancy by nearly 1 year (European Environmental Agency 2017).

One important component of AAP is ultrafine particles (UFP), defined by their aerodynamic size < 100 nm. They are either emitted directly or formed from precursor gases. In urban areas, UFP exposure mostly originates from combustion processes by motorized vehicles, with peak concentrations at the curbside, which are up to tenfold higher than background concentrations, and reach background concentrations within 150 m perpendicular to the road (Karner et al. 2010). Due to their small size, UFP can be inhaled deeply into the lungs, enter the alveoli and penetrate biological membranes, enabling them to pass into the systemic circulation, overcome the placental barrier and finally diffuse into all organ systems including the brain and nervous system (HEI 2013). Toxicological studies suggest that UFP exert a higher toxicity per mass

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00038-019-01202-7) contains supplementary material, which is available to authorized users.

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unit than larger particles and may contribute to the development and progression of various diseases (HEI 2013).

Epidemiological evidence for health effects of UFP is still relatively scarce (HEI 2013). Hypothesized health effects of UFP include cardiovascular and respiratory morbidity and mortality, the elicitation of local pulmonary and systemic inflammation and oxidative stress, and adverse actions on the brain and the metabolism (HEI 2013). However, an increasing number of epidemiological studies examining the exposure of the population and health effects of UFP have been published in the last decade, necessitating a reevaluation of the evidence. Therefore, the aims of this study are to systematically review the epidemiological literature published since the last comprehensive review by the HEI (2013). A special focus is put on studies that have conducted multi-pollutant models to be able to disentangle possible effects of UFP from other pollutants.

Methods

We systematically searched the Medical Literature Analysis and Retrieval System Online (MEDLINE) and the LUDOK database for eligible studies investigating health effects of UFP for the period 01.01.2011 until 11.05.2017. We focused on epidemiologic studies with quantifiable measures of at least one UFP measure/metric in association with health outcomes, published in English or German. Study information was extracted by means of an adapted version of the Quality Assessment Tools of the National Heart, Lung and Blood Institute of Health (2014). For details, see Online Resource. Major differences in study group characteristics and exposure assessment techniques leaving too few studies per single endpoint impeded a formal meta-analysis.

Results

Literature search

Together, the MEDLINE search yielded 1446 references. The search in the LUDOK database yielded 106 references. Another eight references were identified through hand search in other sources, yielding an overall total of 1484 unique references that were examined for inclusion and exclusion criteria. Out of the 1484 identified unique references, 1399 were excluded, leaving an overall number of 85 original references for further evaluation (Online Resource).

Study characteristics

Overall, 85 studies were identified (Table 1). The majority of studies were related to the investigation of short-term effects ($n = 75$) assessing exposures during hours to weeks. Ten studies investigated long-term associations using exposure estimates averaged over a period of months to several years. Short-term studies were dominated by repeated measures panel studies ($n = 31$), scripted exposure studies (participants are exposed to predefined settings, e.g., commuting by bike $n = 16$) and time series studies ($n = 11$). The studies with a long-term study design consisted of cohort studies ($n = 4$), cross-sectional studies ($n = 4$), and one case–cohort and case–control study each.

Exposure assessment

In most studies, UFP were assessed as particle number concentration (PNC) per volume, only few studies measured particle mass or lung-deposited surface area. For PNC, lower cut points ranged between 3 nm and 250 nm (Online Resource). One-third of the studies investigated particles below 100 nm. Other pollutants were assessed in 78 studies, but only 34 studies adjusted for co-pollutants in the statistical analysis. Five studies considered transportation noise as a possible confounder. Measures of UFP or quasi-UFP were in most cases moderately correlated with other pollutants, with highest correlations generally for NO_2 (e.g., Stafoggia et al. 2017); however, some studies also observed negative correlations of PM_{10} with size fractions below 50 nm (Leitte et al. 2012).

Short-term health effects

Mortality

For all-cause mortality, two out of four studies found positive estimates in analyses unadjusted for co-pollutants (Fig. 1, Online Resource). Of these two, one study assessed particle number concentration of particles sized 250–1000 nm in Shenyang, China, with particles in size ranges between 250 and 400 nm showing consistent associations after adjustment for various co-pollutants and ambient temperature (Meng et al. 2013). In the other study, elevated point estimates for lag 4 to lag 6 decreased toward the null upon adjustment for six different co-pollutants (Stafoggia et al. 2017). The strongest influence on the estimates was exerted by adjustment for $PM_{2.5}$ and NO_2.

The evidence of respiratory mortality was also scarce and inconsistent. Out of the five studies on respiratory mortality, four studies found positive though nonsignificantly elevated point estimates for UFP or quasi-UFP. In

Table 1 Summary of study characteristics of the 85 included studies by long-term, short-term and total number of studies, ultrafine particle review, Germany 2018

Characteristics	Short term		Long term		Total	
	n	%	*n*	%	*n*	%
Study location[a]						
Africa	1	1.3	–	–	1	1.2
America, North	30	39.5	7	70.0	37	43.0
America, Middle/South	1	1.3	–	–	1	1.2
Asia, Southeast	1	1.3	–	–	1	1.2
Europe: Eastern	2	2.6	–	–	2	2.3
Europe: Western/Southern	24	31.6	3	30.0	27	31.4
Pacific, Western	12	15.8	–	–	12	14.0
Multiple study regions[b]	5	6.6	–	–	5	5.8
Study design						
Case–cohort	–	–	1	10.0	1	1.2
Case–control	–	–	1	10.0	1	1.2
Cohort	4	5.3	4	40.0	8	9.4
Cross-sectional	4	5.3	4	40.0	8	9.4
Panel	32	42.1	–	–	32	37.6
Case–crossover	8	10.5	–	–	8	9.4
Scripted exposure	16	21.1	–	–	16	18.8
Time series	11	14.5	–	–	11	12.9
Exposure assessment technique						
Model-based	2	2.7	9	90.0	11	12.9
Measurement-based	73	97.3	1	10.0	74	87.1
Exposure assessment model/measurement						
Chemical transport model	–	–	3	30.0	3	3.5
Land-use regression model	–	–	1	10.0	1	1.2
Dispersion model	1	1.3	–	–	1	1.2
Microscale personal exposure model	2	2.7	–	–	2	2.4
Central site measurement	45	60.0	–	–	45	52.9
Residential measurement	2	2.7	–	–	2	2.4
Mobile measurement	17	22.7	–	10.0	17	20.0
Other	3	4.0	1	50.0	4	4.7
Combination of different methods	5	6.7	5		10	11.8
Exposure metric[c]						
UFP	9	12.1	5	50.0	14	16.7
Quasi-UFP	46	62.1	5	50.0	51	60.7
UFP + quasi-UFP	19	25.7	–	–	19	22.6
Outcome type[d]						
Mortality	7	8.8	1	10.0	8	8.9
Morbidity	7	8.8	4	40.0	11	12.2
Emergency	11	13.8	–	–	11	12.2
Subclinical	55	68.8	5	50.0	60	66.7
Outcome—organ-related[d]						
Total mortality	4	3.6	1	7.7	5	4.1
Cardiovascular[c]	47	42.7	4	30.8	51	41.5
Respiratory/atopy[a]	24	21.8	1	7.7	25	20.3
Inflammation	26	23.6	3	23.1	29	23.6
Oxidative stress	4	3.6	–	–	4	3.3

Table 1 (continued)

Characteristics	Short term		Long term		Total	
	n	%	*n*	%	*n*	%
Neurocognitive	3	2.7	1	7.7	4	3.3
Other	2	1.8	3	23.1	5	4.1

[a]Classification of study regions adapted by the World Health Organization regional office scheme

[b]Multiple study regions consist of 17 Southern/Western European study locations and 4 Eastern European study locations

[c]One study did not report any information on ultrafine particles/quasi-ultrafine particle size fractions

[d]Three studies analyze several types of outcome measures and were assigned to two different outcome types. Thus, the studies do not sum up to 85 studies that include mortality

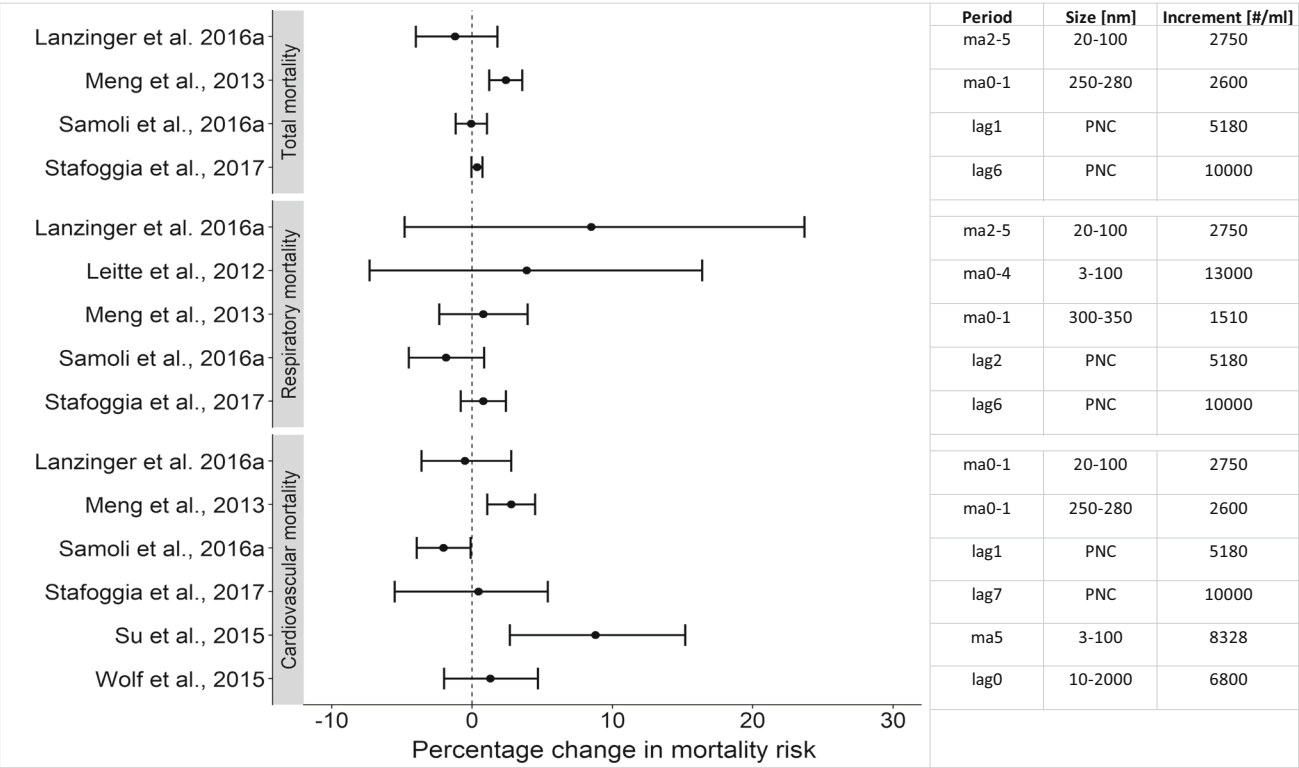

Fig. 1 Percent change in *total and cause-specific mortality* in studies on short-term exposure to ultrafine and quasi-ultrafine particles published between 01/2011 and 05/2017. If available, estimates for the UFP size fraction are shown; otherwise, the size fraction with the most consistent results is shown here, UFP review, Germany 2018

the study by Leitte et al. (2012) in Beijing, China, several size fractions, lag times and averaging periods were systematically assessed. Lag 2 of total PNC and the 4- and 5-day average of the largest particle size fraction (300–1000 nm) were significantly associated with respiratory mortality, while smaller particles, specifically UFP, were not associated. Meng et al. (2013) and Stafoggia et al. (2017) both observed higher estimates in the warm season compared to the cold season. Three studies adjusted for co-pollutants resulting in stronger associations after adjustment for NO_2 in one study (Lanzinger et al. 2016) and small or no changes in quasi-UFP, respectively, total PNC associations after adjustment for NO_2, SO_2 or $PM_{2.5}$, respectively, other source factors (Leitte et al. 2012; Samoli et al. 2016).

Similar to the overall results for respiratory mortality, associations of UFP/quasi-UFP with cardiovascular mortality were inconsistent. Out of the six studies, three studies observed positive associations with cardiovascular mortality (two of them observing at least one significant association), two studies showed no effect, while one study observed negative associations. The study of Su et al.

(2015) in Beijing before and after the Olympic Games systematically looked at different size fractions in the ultrafine range and observed clear adverse associations in the size fractions > 30 nm, but not below. Positive associations in Meng et al. (2013) and Wolf et al. (2015) were observed for particles larger > 250 nm or total PNC, respectively. In the three multi-pollutant studies, adjustment for NO_2 led to a decrease in effect estimates, causing loss of significance in one study (Su et al. 2015) and a decrease to an inverse relationship in the other study (Lanzinger et al. 2016). Adjustment for $PM_{2.5}$ or for sources only caused smaller or no changes in UFP effect estimates (Samoli et al. 2016).

The evidence adds to eleven mostly time series studies reviewed by the HEI panel (2013), reporting positive associations in six studies. The HEI reported strongest associations for cardiovascular mortality and larger UFP size fractions, albeit stating that differing results among specific outcomes and lag structures provide an overall inconsistent pattern.

Emergency department visits and hospital admission

The evidence base for UFP-related effects on utilization of the healthcare system due to respiratory symptoms is limited with six studies investigating adult or pediatric asthma-related visits or admissions (Fig. 2; Online Resource). Most studies observed at least one positive association among several lags and averaging times, but only one study found robust positive associations of UFP mass of mainly residential wood combustion with respiratory visits in Chile (Diaz-Robles et al. 2014). Associations seem to be most probable for children as a susceptible subgroup (Evans et al. 2014; Samoli et al. 2016). For example, in Samoli et al. (2016), associations of PNC of different sizes (total and nucleation mode) and sources (secondary, traffic) with total respiratory admissions had no or negative, whereas most had positive associations (however, with wide confidence intervals) for pediatric hospital admissions. In multi-pollutant models, conducted in five studies, most associations were attenuated toward the null or to inverse associations. Specifically adjustment for NO_2 led to the largest decreases in effect estimates (Online Resource).

Most of the seven studies investigating cardiovascular disease-related use of the healthcare system indicate weak positive associations. No clear time pattern across different studies was visible, even though some studies observed effects preferably within the first 24 h (Gardner et al. 2014; Rosenthal et al. 2013; Samoli et al. 2016). The study by Wolf et al. (2015) suggests that participants with preexisting cardiovascular disease might be more susceptible to adverse associations with elevated UFP/quasi-UFP concentrations. These associations were attenuated upon adjustment for co-pollutants in three available studies with no clear evidence for independent associations of UFP/quasi-UFP. Similarly to respiratory outcomes, adjustment for NO_2 had the strongest effect on the point estimates.

Prior evidence from the HEI review (2013), evaluating 15 studies on acute cardiorespiratory morbidity was inconclusive, due to the heterogeneity of the study designs and the related results. Irrespective of these dissimilarities, the review reported positive associations in ten of the studies.

Other morbidity outcomes

Of the six studies investigating short-term effects of UFP/quasi-UFP on various morbidity outcomes (Online Resource), including general or respiratory symptoms, arrhythmia events and mental discomfort, only one study observed significantly elevated estimates with a marker of perceived stress (Mehta et al. 2015). None of the above-mentioned studies adjusted for co-pollutants or were by design able to disentangle the independent effects of different constituents of the air pollution mixture.

Subclinical endpoints

Lung function-related indices such as peak flow rates and lung volumes were investigated by eleven studies (Table 2; Online Resource). Overall, four of eleven studies conducted with healthy adults and one study conducted with allergic or atopic children showed significant positive associations. Three of these studies applied a scripted exposure design with participants exposed to predefined settings, e.g., commuting by bike, measuring lung function immediately or 2 h after exposure. Two studies with adjustment for co-pollutants observed similar effects upon adjustment for $PM_{2.5}$ and PM_{10}, but UFP estimates lost significance upon adjustment for NO_2 (Janssen et al. 2015; Strak et al. 2012). These results add to prior inconclusive evidence based on eight studies conducted mostly in the 1990s and using fixed site measured UFP in relation to differing endpoints (HEI 2013).

Associations between exposure to UFP/quasi-UFP and blood pressure indices were investigated in 12 studies, of which four applied multi-pollutant models (Online Resource). Seven out of 12 studies found increases of at least one measure of blood pressure after exposure to various size fractions and lag periods of UFP/quasi-UFP with no consistent patterns across studies regarding latency periods and size fractions. For example, Chung et al. (2015) observed an increase of 2.40 mmHg ($p = 0.03$) per concurrent 10,000 particles sub-micrometer PNC exposure. Two studies conducted in China reported inconsistent

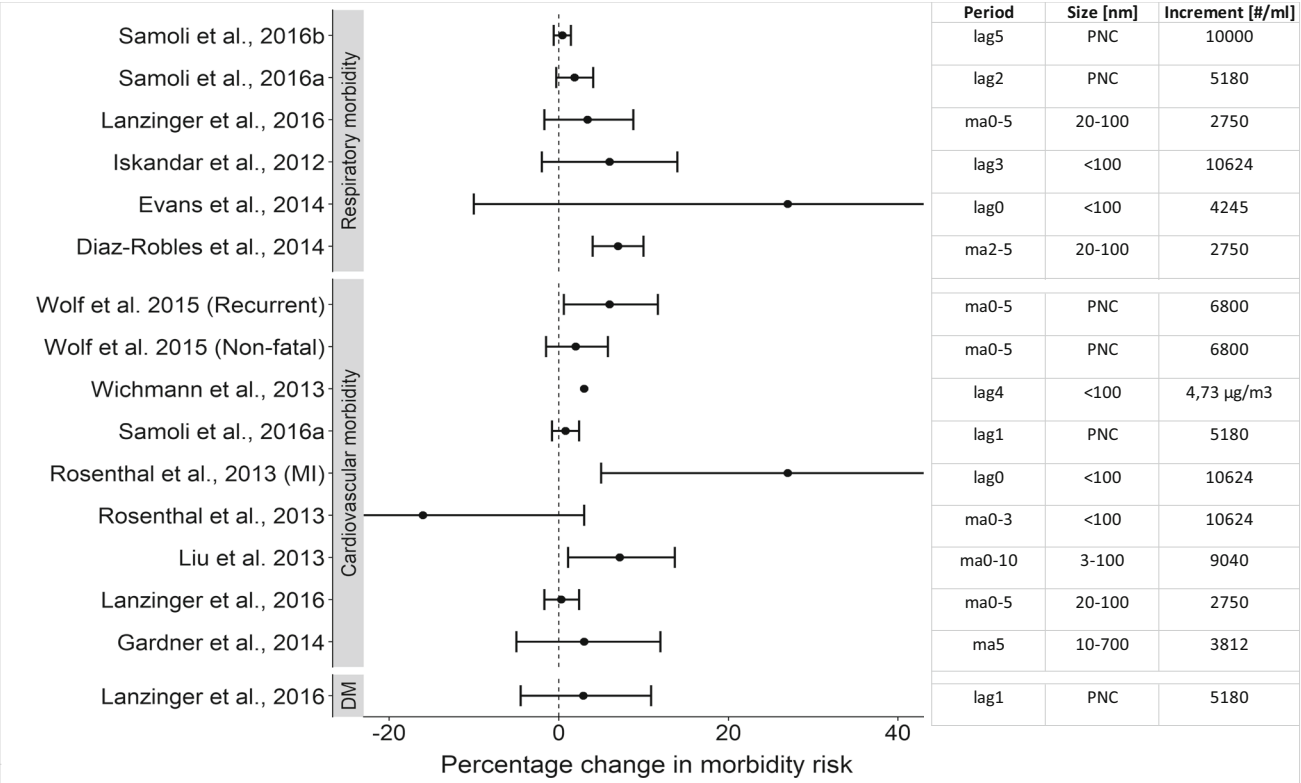

Fig. 2 Percent change in cause-specific *emergency department visits or hospital admissions* for short-term exposure to ultrafine and quasi-ultrafine particles, studies published between 01/2011 and 05/2017. If available, estimates for the UFP size fraction are shown; otherwise, the size fraction with the most consistent results is shown here, UFP review, Germany 2018

Table 2 Summary table of conducted analyses in the 55 studies on subclinical outcomes, ultrafine particle review, Germany 2018

Outcome	Number of studies	Number of studies with single-pollutant associations in expected direction[a]	Number of studies with multi-pollutant associations in expected direction
Respiratory indices	11	4/11	2/3
Blood pressure	12	7/12	2/4
Heart rate variability	16	11/16	4/5
Arrhythmia	1	1/1	Nc
Vascular function	7	4/7	1/2
Pulmonary inflammation	12	11/12	5/5
Systemic inflammation (incl. fibrinogen)	20	8/20	2/5
Neurocognitive outcomes	2	1	Nc

Nc not conducted

[a]Studies showing mostly consistent results with at least one significant effect estimate

patterns depending on adjustment sets, lag periods and specific endpoints (Gong et al. 2014; Zhang et al. 2013). The four multi-pollutant studies showed inconsistent results: Two studies (Pieters et al. 2015; Weichenthal et al. 2014) found similar associations upon adjustment for $PM_{2.5}$, respectively, adjustment for particulate and gaseous pollutants, whereas Rich et al. (2012) and Zhang et al. (2013) observed attenuated effect estimates when adjusting for accumulation mode particle concentration, respectively, NO_2. The prior HEI review (2013) identified four studies, of which three showed overall positive associations between PNC and blood pressure indices.

A relatively large body of new evidence is available for heart rate variability (HRV)-related indices with overall 16 studies (Online Resource). Eight of these studies on HRV were conducted in susceptible subgroups, i.e., patients with

diabetes or coronary artery disease. The reviewed studies present suggestive results with eleven studies showing UFP-related associations for at least one selected outcome measure and five with no associations. Most associations of UFP or quasi-UFP with indicators of HRV were within a short time frame (5 min to 95 h), with two studies showing changes within minutes of increased exposure (Hampel et al. 2014; Peters et al. 2015). For example, concurrent 5-min SDNN decreased by 0.56% (− 1.02%; − 0.09%) with an increase in personal PNC of 16,000 particles (Peters et al. 2015). Two- or multi-pollutant models showed inconsistent changes (Peters et al. 2015; Rich et al. 2012; Weichenthal et al. 2014) upon adjustment for $PM_{2.5}$. Adjusting for NO_2 and O_2 led to similar (Sun et al. 2015) or decreased effect estimates (Weichenthal et al. 2014; Zhang et al. 2013). Prior limited evidence from the HEI (2013) was based on six studies of which three reported associations.

Vascular function has been assessed within seven studies with mostly small sample sizes and often highly selected participants, four studies observed associations in the expected direction, whereas other studies showed only selected or no associations (Online Resource). Two of the seven studies applied two-pollutant models, showing inconsistent results. Prior evidence reported in the HEI review consisted of two studies which showed little associations with PNC, supporting our overall mixed results.

Overall 12 new studies, with seven panel studies and five scripted exposure studies, investigated UFP-related effects on pulmonary inflammation markers (Online Resource). All nine studies assessing FeNO in relation to PNC of different size fractions and $PM_{0.18}$ observed increased FeNO values specifically in response to short-time lagged UFP exposures. Further three studies assessed malondialdehyde (MDA) in exhaled breath condensate, a marker of pulmonary oxidative stress, showing inconsistent (Gong et al. 2014; Sarnat et al. 2014) or nonsignificant positive (Zhang et al. 2016) associations. Another four studies assessing exhaled breath condensate nitrite + nitrate showed higher concentrations (except for Manney et al. 2012) and were strongest for shorter lag periods, i.e., immediately after exposure (Laumbach et al. 2014) or in 0- to 2-day lagged exposures (Gong et al. 2014). Two-pollutant models were conducted in five studies observing similar (Gong et al. 2014; Han et al. 2016; Zhang et al. 2013) or even stronger (Janssen et al. 2015; Strak et al. 2012) effect estimates upon adjustment for NO_2. Adjustment for $PM_{2.5}$ led to unchanged (Strak et al. 2012) or attenuated (Janssen et al. 2015) effect estimates. Out of the six scripted exposure studies evaluated in the prior review (HEI 2013), four studies reported positive associations between pulmonary inflammation markers and UFP of various size fractions, which adds to the overall evidence for an association of UFP with local pulmonary inflammatory responses.

Overall 20 studies examined UFP-related effects on systemic inflammation, with one cohort, two cross-sectional, eleven panel and four scripted exposure studies. Eight of the studies examined susceptible adult groups, e.g., with cardiac symptoms or diabetes, and one of the studies examined children. The eleven studies on CRP indicate inverse (Strak et al. 2013), inconsistent (Bind et al. 2012; Fuller et al. 2015) or positive (Croft et al. 2017; Huttunen et al. 2012; Karottki et al. 2014, 2015; Rich et al. 2012; Rückerl et al. 2014; Sarnat et al. 2014; Wang et al. 2016; Wittkopp et al. 2013) associations ranging mostly from slightly inverse to positive associations being significant for single lag periods. For example, Rückerl et al. (2014) reported percent change of 11.7 (3.0; 21.1) per 5722/ml 3-day lagged PNC3-100 nm. Two studies adjusted their models for co-pollutants, leading to decreased effect estimates upon adjustment for $PM_{2.5}$ (Rückerl et al. 2014; Strak et al. 2013) and PM_{10} (Strak et al. 2013) and increased effect estimates upon adjustment for NO_2 (Strak et al. 2013). For fibrinogen, studies report mostly positive associations (Croft et al. 2017; Rich et al. 2012; Wang et al. 2016) being strongest for shorter lag periods, inconsistent effect estimates (Bind et al. 2012; Gong et al. 2014; Zhang et al. 2013) and mostly inverse associations (Huttunen et al. 2012; Strak et al. 2013). In two-pollutant models (four studies), estimates decreased (Strak et al. 2013), increased (Croft et al. 2017) or did not change (Rich et al. 2012) upon adjustment for $PM_{2.5}$ or PM_{10} and decreased after NO_2 adjustment (Strak et al. 2013). Other markers of inflammation, such as blood cell counts, myeloperoxidase, TNFR-II, IL-6, IL-8, IL-12, urinary 8-OHdG, urinary MDA, and serum brain-derived neurotropic factor, were examined in several studies showing mostly positive associations. Overall, many studies indicate positive associations between UFP and inflammation markers, specifically for shorter lag periods. However, the small number of multi-pollutant models does not allow firm statements on independent effects of UFP/quasi-UFP. Previous evidence in relation to systemic inflammation markers was mixed with four out of eight studies reporting significant associations with CRP, two out of seven studies reporting associations between PNC and fibrinogen as well as mixed results of single studies assessing other inflammatory-related endpoints (HEI 2013).

Long-term health effects

Morbidity and mortality

New evidence has emerged since the last review with overall ten studies investigating for the first time long-term

effects of UFP on various health outcomes, mainly based on chemical transport or land-use regression models (Table 3, Online Resource). One cohort study with 101,884 female participants from the California Teachers Study observed a significantly elevated risk of IHD mortality and positive associations for all-cause *mortality*, cardiovascular mortality and pulmonary mortality (Ostro et al. 2015). The study examined two-pollutant models by adjusting one UFP constituent for each of the other constituents. Therefore, an evaluation of UFP effects adjusted for other air pollutants as, e.g., $PM_{2.5}$ or NO_2, was not possible.

Increased odds for low birthweight (LBW) in term-born infants (> 37 gestational weeks) was associated with submicron particle mass $PM_{0.1}$ (Laurent et al. 2014). Using source apportionment, gasoline, followed by wood burning, meat cooking, diesel and high-sulfur sources were most strongly associated with term LBW. In a similar study setting with the same exposure assessment, the authors partly confirmed their results with a case–cohort approach and additionally found significantly elevated ORs for preterm birth (Laurent et al. 2016a, b). A recent study found positive, yet nonsignificant, associations between time-activity-adjusted PNC exposure (> 4 nm) at each residential address and self-reported prevalence of stroke, ischemic heart disease, hypertension and diabetes (Li et al. 2017). Since none of the above studies adjusted for co-pollutants, evaluation of independent effects was not possible.

Subclinical outcomes

Out of the three cohort studies and two cross-sectional studies investigating long-term health effects on subclinical

Table 3 Summary table of conducted analyses in the ten long-term studies, ultrafine particle review, Germany 2018

Outcome type/study	Outcome	Single-pollutant associations	Multi-pollutant associations
Mortality/Ostro et al. (2015)	All-cause	HR 1.01 (0.98; 1.05)	Nc
	Cardiovascular/	HR 1.03 (0.97; 1.08)/	
	IHD	HR 1.10 (1.02; 1.18)	
	Pulmonary	HR 1.01 (0.93; 1.10)	
Morbidity/Li et al. (2017)	Stroke/IHD	OR 1.35 (0.83; 2.22)	Nc
Laurent et al. (2014)	Low birth weight	OR 1.03 (1.02; 1.03)/	Nc
Laurent et al. (2016b)	Low birth weight	OR 1.00 (0.98; 1.01)/	Nc
	($PM_{0.1}$/PNC)	OR 1.00 (0.99; 1.01)	
Laurent et al. (2016a)	Preterm birth	OR 1.02 (1.02; 1.03)/	Nc
	($PM_{0.1}$/PNC)	OR 1.00 (0.99; 1.00)[a]	
Subclinical/Aguilera et al. (2016)	Carotid intima–media thickness (PNC/LDSA)	2.06% (0.03; 4.10)/	PM_{10}: 2.13% (− 2.31; 6.57)
		2.32% (0.23; 4.48)	
Viehmann et al. (2015)	hs-CRP/	3.8% (0.6; 8.4)/	$PM_{2.5}$: 0.63% (− 3.6; 4.86)
	Fibrinogen/	1.0% (0.0; 2.0)/	
	WCC	1.0% (− 0.1; 2.1)	LDSA: 3.35% (− 0.20; 6.90)
Lane et al. (2015)	hs-CRP/	β 1.26 (− 0.02; 2.75)/	
	IL-6	β 0.65 (− 0.26; 1.55)	
Lane et al. (2016)	hs-CRP/IL-6/	9.8% (− 8.3; 31.4)/5.8% (− 5.6; 18.5)/	Nc
	TNFRII/Fibrinogen	3.6% (− 1.9; 9.4)/− 1.9% (− 5.5; 1.6)	
Sunyer et al. (2015)	Working memory	β − 4.9 (− 10; 0.22)	Nc
	Superior working memory	β − 5 (− 9.1; − 0.96)	
	Inattentiveness	β 3.9 (0.31; 7.6)	

IHD Ischemic heart disease, *PM* particulate matter, *PNC* particle number concentration, *LDSA* lung-deposited surface area, *hs-CRP* high-sensitive C-reactive protein, *IL* interleukin, *TNRF* tumor necrosis factor, β difference, *Nc* not conducted

[a]Geocoded at tax parcel level: 1.03 (1.02; 1.04)

outcomes, one study adjusted for co-pollutants (Table 3, Online Resource). Aguilera et al. (2016) observed cross-sectional associations of land-use regression model PNC 10-300 and LDSA with carotid intima–media thickness in 1503 participants of the SAPALDIA cohort. Upon adjustment for NO_2, the association with LDSA remained significant, while the effect estimate for PNC changed direction. Two studies observed increased effect estimates for inflammatory biomarkers (hs-CRP, IL-6, TNFIII, fibrinogen and WBC) within a time window of 1 year (Lane et al. 2015; Viehmann et al. 2015), while one study (Lane et al. 2016) reported nonsignificant negative estimates for fibrinogen. A Spanish cohort study in the framework of the BREATHE (Brain Development and Air Pollution Ultrafine Particles in School Children) project investigating quasi-UFP effects (10–700 nm) observed a smaller increase in the 12-month development of cognitive function of 2715 children attending schools in highly polluted areas compared to areas with low pollution (Sunyer et al. 2015). Quasi-UFP exposure at the school was inversely related to working memory and attention. Overall, the diverse outcomes make it impossible to draw any firm conclusions.

Discussion

This systematic review of epidemiological studies on health effects of UFP and quasi-UFP presents increasing suggestive evidence for independent short-term health effects on inflammation, autonomic tone and blood pressure (Table 4). The evidence is inconsistent or insufficient to draw firm conclusions on mortality and morbidity or on long-term effects of UFP. One of the most important aspects in the investigation of UFP-related health effects is the exposure assessment, with traditional methods of air pollution exposure assessment not being optimally designed to assess the true high spatial and temporal variability of UFP, most likely biasing effects toward the null. Moreover, the scarcity of studies with multi-pollutant models limits the evaluation of independent effects. Because size ranges of particles, lag periods and averaging times for exposure differ between studies, it is difficult to compare effects sizes and consistency between studies.

Our evaluation of the health relevance of UFP is based on 85 epidemiologic studies published since 2011 and therefore represents an update of the last comprehensive review conducted by the HEI in 2013, which concluded that "the current database of experimental and epidemiologic studies does not support strong and consistent conclusions about the independent effects of UFP on human health" (HEI 2013). In the current review, we use similar design- and outcome-specific categories to be able to integrate our findings with the prior evidence. Since independence of effects is the key question regarding the health relevance of UFP, we specifically focus on studies with co-pollutant adjustment. Epidemiological evidence is quickly increasing, and we expect that the next few years will yield a substantial increase in relevant studies, including studies with more elaborate exposure assessment methods and multi-pollutant models.

Even though results are not consistent across all different measures, the majority of the eleven studies investigating short-term effects on BP indicate an association with increased arterial blood pressure, which may be independent of co-pollutant exposure. Together with a relatively large body of evidence from studies on HRV, it seems likely that short-term exposure to UFP/quasi-UFP changes autonomic tone and therefore adversely influences arterial blood pressure, the most important risk factor for cardiovascular disease. Another potentially contributing pathway to an increased cardiovascular disease risk is an elicitation

Table 4 Summary table of all included studies in single- and multi-pollutant associations, ultrafine particle review, Germany 2018

Outcome	Single-pollutant effect	Consistency of general pattern	Multi-pollutant effect	Consistency of general pattern
Short-term	49/79	21/49	18/32	7/18
Mortality	5/7	2/5	4/6	1/4
Morbidity	3/7	0/3	–	–
Hospital admission	4/10	2/4	0/5	–
Subclinical	37/55	17/37	14/21	6/14
Long-term	8/10	1/1	0/1	–
Mortality	1/1	1/1	–	–
Morbidity	3/4	–	–	–
Hospital admission	–	–	–	–
Subclinical	4/5	–	0/1	–

of pulmonary and systemic inflammation, which was evident specifically for short lag periods of hours to a few days.

We did not find strong and consistent evidence for associations with natural, cardiovascular or respiratory morbidity and mortality, which represents no change to previous evaluations (HEI 2013). The observed effects at least partially overlap with other air pollutant effects, most clearly seen for NO_2. Effects may be larger in the warm season; therefore, possible effect modification by season is an important factor to consider in future short-term effect studies. Even though there are a growing number of specifically designed studies, we could not identify a consistent pattern of health effects on either cardiovascular or respiratory disease risk across the different endpoints including mortality, morbidity and emergency department visits/hospital admissions. For other outcomes such as neurocognitive function or birth outcomes, the evidence base is insufficient to derive conclusions.

For the first time, we could also identify ten studies on long-term effects of UFP on various health outcomes. These studies are mostly based on modeled UFP concentrations, for which only very limited data for an external validation of the model output are available. While most of these studies found elevated point estimates for associations of UFP with adverse health outcomes, it is still unclear to what extent these associations overlap with other pollutants.

The lack of consistent findings for many of the investigated outcomes can be explained by a number of factors. These are mainly related to differences in exposure assessment and assignment, study design, size and population, and different confounder controls, specifically differences in the adjustment for co-pollutants. The exploration and development of alternative exposure metrics, spatial modeling techniques and statistical methods are urgently needed to improve the investigation of UFP-related health effects. Challenges of exposure assessment for UFP include the high spatial and temporal variability of UFP/quasi-UFP, which necessitate different exposure assessment designs than the "classical" air pollutants like $PM_{2.5}$ and PM_{10} with a much more homogeneous spatial distribution. This high spatial variability is of concern not only for long-term health effects studies, which are based on long-term spatial differences in exposure, but also for short-term studies with a central site measurement. These studies assume that the temporal changes from day to day are evenly distributed across the entire study area; an assumption that might not hold true for UFP. Given the possibility of a larger exposure estimation error for UFP compared to other pollutants, a systematic bias toward the null in single- and multi-pollutant studies is probable (Dionisio et al. 2014; Goldman and Mulholland 2010). Important applications are road traffic-related exposures and the emerging issue regarding exposure to UFP in the vicinity of airports, which has only recently been described (Hudda et al. 2016). Confounding by transportation noise or other environmental determinants of health such as green space represents a further knowledge gap. Research is still at the beginning, and new exposure assessment methods need to be defined and employed in epidemiological studies.

A further challenge of UFP/quasi-UFP exposure assessment is the non-standardized equipment and the non-standardized use of size fractions in the studies. The commonly used measurement devices have different lower cut points for particle size. Since the majority of particles are located in the nucleation mode (< 20 nm) of the particle size distribution, even small differences in the lower cut point between 1 and 20 nm can lead to substantial differences in particle number concentration. Furthermore, the reporting of the exposure assessment often does not include the exact size range of particles, which prevents direct comparisons of exposures between studies. Differences in the upper cut point probably contribute less to differences in exposure assessment, as the larger particles (> 100 nm) contribute only to a negligible extent to the overall particle number concentration.

Even though several studies across the investigated endpoints have observed positive associations of UFP/quasi-UFP with various health effects, the overall evidence for independent effects is still insufficient. More recent studies apply multi-pollutant models more often than older studies, which is a positive development (e.g., Aguilera et al. 2016; Croft et al. 2017; Lanzinger et al. 2016; Samoli et al. 2016b; Stafoggia et al. 2017). However, the type of adjustment still varies substantially between studies and there is no standard strategy for co-pollutant adjustment yet. At the moment, adjustment for NO_2 generally seems to exert a greater effect on the point estimate than other co-pollutants (Lanzinger et al. 2016; Samoli et al. 2016; Su et al. 2015; Zhang et al. 2013). One reason for this is the overlap in sources and spatial/temporal distribution of UFP/quasi-UFP and NO_2, which can lead to instability in the models and biased effect estimates in two-exposure models, with higher estimates for those pollutants with lower measurement error and lower or even inverse associations for pollutants with high measurement error.

Conclusions

The evidence suggests adverse associations of short-term UFP exposure with pulmonary and systemic inflammation, autonomic tone and blood pressure, which may be at least partly independent of other pollutants. For the other studied health outcomes, the evidence on independent health

effects of UFP remains inconclusive or insufficient. A future challenge is the development of enhanced spatiotemporal models which can contribute to a more precise exposure assessment across larger areas as well as incorporating multi-pollutant models to elucidate the independence of effects.

Funding The study was supported by the German Environmental Agency (Project Number: Grant 00377 7205-2 UKAGEP) and the Swiss Federal Office for the Environment (Contracts No 110001982/8T20/13.0077.PJ/0003/M461-2794 and 00.5082.PZ 1-0389. Financial support was provided by the Swiss Federal Ministry of Education and Research.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Human and animal rights This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Informed consent was not applicable.

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