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Respiratory Health Effects of Ultrafine Particles in Children: A Literature Review

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Abstract

By convention, airborne particles ≤0.1 μm (100 nm) are defined as ultrafine particles (UFPs). UFPs can comprise a large number of particles in particulate matter with aerodynamic diameters ≤2.5 μm ($PM_{2.5}$). Despite the documented respiratory health effects of $PM_{2.5}$ and concerns that UFPs might be more toxic than larger particular matter, the effects of UFPs on the respiratory system are not well-described. Even less is known about the respiratory health effects of UFPs among particularly vulnerable populations including children. We reviewed studies examining respiratory health effects of UFPs in children and identified 12 relevant articles. Most (8/12) studies measured UFP exposure using central ambient monitors, and we found substantial heterogeneity in UFP definitions and study designs. No long-term studies were identified. In single pollutant models, UFPs were associated with incident wheezing, current asthma, lower spirometric values, and asthma-related emergency department visits among children. Also, higher exhaled nitric oxide levels were positively correlated with UFP dose among children with asthma or allergy to house dust mites in 1 study. Multivariate models accounting for potential co-pollutant confounding yielded no statistically significant results. Although evidence for a relationship between UFPs and children's respiratory is accumulating, the literature remains inconclusive. Interpretation of existing data is constrained by study heterogeneity, limited accounting for UFP spatial variation, and lack of significant findings from multi-pollutant models.

Keywords

ultrafine; child; particulate matter; respiratory health

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1. Introduction

Over the past several decades, the adverse health effects of airborne particulate matter have been clearly established in the literature.(EPA, 2009) Numerous studies have documented increases in respiratory and cardiovascular diseases and overall mortality associated with both short-term and long-term exposure to higher levels of particulate matter, especially particulate matter with aerodynamic diameters ≤2.5 μm ($PM_{2.5}$).(IOM, 2000; Chung et al., 2015; HEI, 2013; Pope and Dockery, 2006) Both $PM_{2.5}$ and PM_{10} (particulate matter with aerodynamic diameters ≤10 μm) are regulated by the United States Environmental Protection Agency (EPA) as criteria pollutants under the Clean Air Act. Substantial evidence has also demonstrated an association between residential proximity to major roadways, exposure to traffic-related air pollution (TRAP), and a variety of adverse health effects.(Boehmer et al., 2013; Boothe et al., 2014; Bowatte et al., 2014; Laumbach and Kipen, 2012)

Ultrafine particles (UFPs), which include carbonaceous or metallic particles less than or equal to 0.1 μm (100 nm) in size, are an important component of $PM_{2.5}$ and PM_{10} as well as TRAP.(HEI, 2013) UFPs typically are generated through combustion of biomass (e.g., tobacco smoking, wood burning, incense burning) or fossil fuels (e.g., coal, natural gas, diesel).(HEI, 2013) UFP concentrations exhibit substantial spatial variation: levels are high near combustion sources but rapidly decay with distance.(Karner et al., 2010; HEI, 2013; Pekkanen and Kulmala, 2004) UFPs form a small proportion of the total mass of $PM_{2.5}$ and PM_{10}, but they can comprise a large majority of the total particle count of both $PM_{2.5}$ and PM_{10}.(Nazaroff, 2004; HEI, 2013) However, UFPs are not an EPA criteria pollutant and are therefore not routinely monitored at most air pollution monitoring stations in the United States.

Although UFPs are short-lived in the environment (e.g., some quickly accumulate into larger particles, others can evaporate),(HEI, 2013) UFPs might be more toxic than larger particulate matter for several reasons. First, their small diameter enables UFPs to penetrate deep into the lungs more easily than larger particles.(HEI, 2013) Airway deposition models have demonstrated that while the majority of larger particles deposit in the extrathoracic region and bronchi, UFPs deposit at much higher rates in the bronchioles and alveoli. (Kreyling et al., 2006; HEI, 2013) Second, UFPs are cleared less efficiently from the respiratory tract than larger particles and thus have more opportunity to translocate from the lung into the bloodstream and into other organ systems.(HEI, 2013) Third, UFPs have a greater surface area to mass ratio compared to larger particles, providing a larger area to adsorb potentially toxic chemicals or metals and interface with pulmonary surfaces. Given these features, some researchers have hypothesized that the ultrafine component of particulate matter might be responsible for many of the observed health effects of $PM_{2.5}$ and PM_{10}.(HEI, 2013; Terzano et al., 2010)

Despite these considerations, the health effects of UFPs remain unclear, particularly for children.(EPA, 2009; HEI, 2013; Schuepp and Sly, 2012) The importance of this information is highlighted by the large body of evidence linking air pollution to a range of adverse respiratory effects in children, including decreased lung function growth, increased

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respiratory infections, higher asthma incidence, and elevated risk of asthma exacerbations. (IOM, 2000; EPA, 2009; Gauderman et al., 2015) Although the contribution of UFPs to these associations is still uncertain, the vulnerabilities of children are well-known.(EPA, 2009; Schuepp and Sly, 2012) The majority of lung alveoli are formed after birth, so early childhood exposures could affect lung development and have long-term consequences. (Gauderman et al., 2015; Schuepp and Sly, 2012) Children have higher minute ventilation and pulmonary surface area to body mass ratios, so their potential effective pollutant dosage is higher than that of adults.(EPA, 2009; Schuepp and Sly, 2012) Children's breathing zones are also often closer to the ground and therefore closer to sources of motor vehicle exhaust. (Schuepp and Sly, 2012)

Given the prevalence and high potential for toxicity of UFPs in children, we sought to review the existing literature regarding the respiratory health effects of UFPs in children. Herein, we describe the current state of evidence on this topic.

2. Methods

In February 2015, we searched PubMed/Medline, Embase, CAB Abstracts, Scopus, and ProQuest Environmental Science Collection for studies using the search terms “ultrafine,” “child*,” and “respiratory” or “asthma.” Additional sources of relevant articles were reference lists of publications identified in our initial search, the EPA's 2009 Integrated Science Assessment for Particulate Matter, and the Health Effects Institute's 2013 review on ambient UFPs.(EPA, 2009; HEI, 2013) Inclusion criteria for articles were (1) publication in a peer-reviewed journal; (2) inclusion of UFPs as an exposure; (3) inclusion of respiratory health effects (such as asthma incidence, asthma exacerbations, respiratory symptoms, medical visits and hospitalizations) as an outcome; (4) investigation of associations between UFPs and respiratory health effects; and (5) inclusion of children in the study. Articles were excluded if they (1) were not available in English; (2) did not involve humans; (3) did not specifically analyze children under 18 years; (4) did not separate UFPs from larger particle sizes when reporting exposures; or (5) exclusively examined engineered nanoparticles.

We abstracted information on study design, exposure assessment, respiratory health outcome, and results (including relevant effect estimates when available) from included studies.

3. Results

Twelve studies met our specified selection criteria.(Andersen et al., 2008a; Andersen et al., 2008b; Buonanno et al., 2013; Diaz-Robles et al., 2014; Evans et al., 2014; Halonen et al., 2008; Iskandar et al., 2012; Kim et al., 2011; Newcomb et al., 2012; Pekkanen et al., 1997; Spickett et al., 2014; Tiittanen et al., 1999) Half originated in Scandinavia.(Andersen et al., 2008a; Andersen et al., 2008b; Halonen et al., 2008; Iskandar et al., 2012; Pekkanen et al., 1997; Tiittanen et al., 1999) All were observational epidemiologic studies except one, which used a case-crossover design to compare UFP exposures indoors and outdoors.(Newcomb et al., 2012) We did not find any exposure chamber studies examining the respiratory health effects of UFPs in children.

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3.1 Ultrafine Particle Exposure Measurement

Almost all studies measured UFP exposure using particle number concentration (expressed as number of particles per cm^3); one study (Diaz-Robles et al., 2014) used particle mass concentration. Using various condensation particle counters (Table 1, 2, and 3), most studies (8/12) in this review used a maximum particle diameter size of 0.1 μm to define UFPs. (Andersen et al., 2008b; Diaz-Robles et al., 2014; Evans et al., 2014; Halonen et al., 2008; Iskandar et al., 2012; Pekkanen et al., 1997; Spickett et al., 2014; Tiittanen et al., 1999) Of the remaining 4 articles, particles were considered UFPs if they were 0.01–0.3 μm (Buonanno et al., 2013), 0.01–0.7 μm (Andersen et al., 2008a), or ≤1 μm in diameter.(Kim et al., 2011; Newcomb et al., 2012)

Most studies (8/12) estimated UFP exposure by measuring outdoor particle concentrations at one or more central monitoring stations (central ambient exposure assessment).(Andersen et al., 2008a; Andersen et al., 2008b; Diaz-Robles et al., 2014; Evans et al., 2014; Halonen et al., 2008; Iskandar et al., 2012; Pekkanen et al., 1997; Tiittanen et al., 1999). Given the spatial variability of UFPs and subsequent challenges in exposure measurement, associations between central monitoring data and acute health effects (e.g., incident wheeze, asthma-related hospitalizations) might be less subject to exposure missclassification than investigations of chronic (long-term) health effects.(Ostro et al., 2015)

Among the 8 articles with central monitoring data, 5 articles reported means, 2 reported medians, and 1 reported both means and medians. Of the 5 reporting means, UFP number concentrations ranged from 5,151–29,100 particles/cm^3 (Evans et al., 2014; Pekkanen et al., 1997); 1 of these 5 measured mean UFP mass concentration (8 μg/m3; range, 1.6–25.8). (Diaz-Robles et al., 2014) Instead of means, Tiittanen et al., 1999 and Halonen et al., 2008 reported median UFP levels (14,700 and 8,203 particles/cm^3, respectively). Both mean and median UFP number concentrations were reported by Iskandar et al., 2012; mean UFP number concentration was comparable to aforementioned studies with averaged central monitoring data (6,398 particles/cm^3), but median UFP number concentration was lower than other reports (5,839 particles/cm^3).

Among the remaining 4 studies(Buonanno et al., 2013; Kim et al., 2011; Newcomb et al., 2012; Spickett et al., 2014), 1 study measured UFP levels in children's homes(Spickett et al., 2014), another in children's schools(Kim et al., 2011), and a separate study measured UFPs at the site where the study intervention was conducted.(Newcomb et al., 2012) Only 1 study measured exposure using personal UFP monitors.(Buonanno et al., 2013)

3.2 Ultrafine Particles by Microenvironment

Although few studies meeting our selection criteria measured UFPs in microenvironments typical of children, this literature provides valuable insight. An investigation of 37 children's homes in China found that average indoor UFP levels were higher in kitchens (measurement 1, 40,000±26,000 particles/cm^3; measurement 2, 41,000±24,000 particles/cm^3) than in living rooms (measurement 1, 31,000±17,000 particles/cm^3; measurement 2, 31,000±19,000 particles/cm^3) and children's bedrooms (measurement 1, 28,000±15,000 particles/cm^3; measurement 2, 29,000±15,000 particles/cm^3).(Spickett et al., 2014) Compared to homes

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without pets, homes with a cat, dog, or bird had significantly higher average indoor UFP levels in living rooms and children's bedrooms (P = .03 for each).(Spickett et al., 2014) Indoor UFP levels appeared higher in homes with carpet than in homes with wood or concrete flooring, but this difference was not statistically significant.(Spickett et al., 2014) Dwelling age, air conditioning use, and type of furniture were not significantly associated with indoor UFP levels.(Spickett et al., 2014) In addition, study authors observed a nonsignificant trend of higher outdoor UFP levels near apartments than houses.(Spickett et al., 2014) Given the small sample size (n = 37), study power might have limited investigators' ability to detect statistically significant differences.

A study of 12 schools in 3 South Korean cities found that the average indoor UFP level within classrooms was 18,230 particles/cm^3 (standard deviation = 17,300 particles/cm^3). (Kim et al., 2011) Comparing these results to studies of classroom UFP levels that did not measure health outcomes, the South Korean results were much higher than those from rural Canada (5,017 particles/cm^3)(Weichenthal et al., 2008) but comparable to findings from Athens, Greece (24,000 particles/cm^3)(Diapouli et al., 2008) and the Los Angeles metropolitan area of the United States.(Polidori et al., 2013) Investigators did not report any significant associations between indoor UFP levels and building age, classroom population density, classroom shelf space, or amount of textiles in the classroom.(Kim et al., 2011) No schools in the study had a mechanical ventilation system, so variation in UFP levels across different ventilation system types could not be assessed.(Kim et al., 2011)

A study of 103 Italian children performed the most detailed assessments of UFP exposure by microenvironment in this literature and provided valuable insight into potential UFP sources across different microenvironments of children.(Buonanno et al., 2013) Using personal UFP monitors (2-day integrated samples) and time-activity diaries, investigators found that children's homes were the major source (57%) of children's average total daily UFP dose (a calculation that accounted for time spent in each microenvironment, activity type, and child inhalation rate during the activity).(Buonanno et al., 2013) School time contributed 18%, and transportation time contributed 6% to daily UFP dose.(Buonanno et al., 2013) Children with fireplaces at home and children who reported experiencing traffic jams while commuting to or from school had daily UFP doses significantly higher than average (P < .01 for each).(Buonanno et al., 2013) Additionally, these authors explored UFP exposure intensity by relating UFP dose to time spent in each activity and found that cooking/eating had the highest UFP exposure intensity of all activities analyzed.(Buonanno et al., 2013)

3.3 Ultrafine Particles and Other Pollutants

Extensive literature exists on the correlation between UFPs and other pollutants.(HEI, 2013; Karner, 2010) Among the 12 studies included in our review, most (9/12) investigated the respiratory health effects of air pollutants other than UFPs and examined correlations between UFPs and these pollutants. Correlations were generally high for UFPs and nitrogen oxides(Andersen et al., 2008a; Halonen et al., 2008; Pekkanen et al., 1997; Tiittanen et al., 1999), but a minority of studies found lower or non-significant correlations.(Andersen et al., 2008b; Iskandar et al., 2012; Kim et al., 2011) Weak associations (if any) were reported for UFPs and sulfur dioxide.(Kim et al., 2011; Pekkanen et al., 1997; Tiittanen et al., 1999) The

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relationship of UFPs to $PM_{2.5}$ and PM_{10} was not strong; although UFPs were correlated with $PM_{2.5}$ and PM_{10} in 2 studies (Spearman $r > 0.5$)(Pekkanen et al., 1997; Tiittanen et al., 1999), 4 other studies did not support these findings.(Andersen et al., 2008a; Andersen et al., 2008b; Halonen et al., 2008; Iskandar et al., 2012)

Despite strong evidence highlighting the importance of accounting for co-pollutants when investigating the health effects of UFPs(HEI, 2013), we did not find this practice to be consistent in our literature review. Only 1 study that reported a significant association between UFPs and respiratory health effects in children subsequently adjusted for co-pollutants, and that association was no longer significant in multivariate modeling.(Halonen et al., 2008)

3.4 Subjective Respiratory Outcomes

We identified 4 studies investigating the relationship between UFPs and respiratory symptoms in children (Table 1). The first article (Tiitanen et al., 1999) measured UFP number concentration and other air pollutants in the center of a Finnish city and assessed respiratory symptoms among 49 school-aged children with chronic respiratory symptoms who previously participated in the Pollution Effects on Asthmatic Children in Europe (PEACE) study.(Roemer et al., 1999; Tiittanen et al., 1999) Investigators observed a non-significant trend toward higher UFP number concentration and increased child-reported bronchodilator (1–day lag; adjusted daily prevalence of reported bronchodilator use was 0.05 in the highest UFP vs. 0.03 in the lowest UFP tertile, *P* value not published).(Tiittanen et al., 1999) The authors did not find significant relationships between UFPs and child-reported respiratory symptoms or asthma controller medication use, but study power was limited.(Tiittanen et al., 1999)

Within the past decade, 3 additional publications have investigated UFPs and respiratory symptoms in children. Andersen et al., 2008a examined the relationship between incident wheezing, UFPs, and other pollutants in a birth cohort of 205 Danish children aged 0–3 years who participated in the Copenhagen Prospective Study on Asthma in Childhood. (Andersen et al., 2008a) Exposures were assessed at a central monitoring site in Copenhagen (1998–2004). Investigators defined UFP exposure as the number concentration of particles 0.01–0.7 μm in diameter, because they reported that particles <0.01 μm comprised >95% of these total concentration measurements.(Andersen et al., 2008a) They assessed incident wheeze through diary cards completed by children's parents.(Andersen et al., 2008a) Investigators found that UFP exposure was positively associated with incident wheeze among infants (aged 0–1 years) living within 5 km of the central monitor (OR [95% CI] = 2.5 [1.0–5.8], $P < .05$).(Andersen et al., 2008a) Interestingly, UFP exposure was inversely related to incident wheeze among children aged 2–3 years within the same region (OR [95% CI] = 0.4 [0.2–0.8], $P < .05$).(Andersen et al., 2008a) No significant association was found between UFPs and incident wheeze when investigators included data from children living >5 km of the exposure monitoring site in their analysis.(Andersen et al., 2008a) The authors suggested that the altered effect after age 1 year (among children <5 km from the monitoring site) might be attributable to use of respiratory medications among older children, leading to decreased susceptibility to potential pollutant health effects.(Andersen et al., 2008a)

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The most recent studies examining UFPs and respiratory symptoms in children originated in Asia. Kim et al., 2011 conducted the largest study of UFPs and respiratory symptoms in children to date among 2,400 South Korean 4th grade students in 12 urban schools. The investigators sampled air inside and outside of children's classrooms (34 indoor samples, 12 outdoor samples).(Kim et al., 2011) The average indoor UFP level was 18,230 particles/cm^3 (standard deviation = 17,300 particles/cm^3) and the average outdoor UFP level was 16,480 particles/cm^3 (standard deviation = 12,500 particles/cm^3).(Kim et al., 2011) The authors reported a significant positive association between outdoor UFP number concentration at schools and current asthma (self-reported in questionnaires completed by children), with an OR (95% CI) = 1.93 (1.08–3.46) and P = .03.(Kim et al., 2011) No significant associations were found between indoor UFP number concentration (measured within classrooms) and any outcomes (wheeze, physician-diagnosed asthma, or current asthma).(Kim et al., 2011) Sampling of UFPs in a number of locations (within classrooms and outside of each of the 12 schools) was a strength of the study. One consideration that could affect interpretation of these results was that investigators defined particles ≤1 μm as UFPs.(Kim et al., 2011)

Most recently, a cross-sectional study measuring home UFP exposure for 37 children in a southern Chinese city found no significant relationships between overall indoor home levels of UFPs and child respiratory symptoms (assessed by questionnaires administered to children's parents).(Spickett et al., 2014) Sample size could have been limited study power. A strength of the investigation was the variety of locations sampled in the home: the authors performed indoor air sampling in each child's bedroom, living room, kitchen, and doorway/balcony.(Spickett et al., 2014)

Overall, we identified 4 studies examining UFPs and subjective respiratory outcomes in children. Higher UFP number concentration was significantly associated with incident wheezing among Danish infants(Andersen et al., 2008a) and current asthma among Korean schoolchildren.(Kim et al., 2011) A strength of the latter study was the measurement of UFPs at students' physical locations(Kim et al., 2011), given the substantial spatial variability of UFPs.(Karner et al., 2010; HEI, 2013) In contrast, the Danish study relied on central monitoring data.(Andersen et al., 2008a) Neither study identified significant findings from analyses accounting for potential confounding by other pollutants(Andersen et al., 2008a; Kim et al., 2011), limiting interpretability.

3.5 Objective Respiratory Outcomes

Four studies addressed the relationship between UFPs and objective respiratory outcomes (Table 2). All studies performed spirometry, and two also measured exhaled nitric oxide (eNO).(Buonanno et al., 2013; Newcomb et al., 2012)

The earliest publications on this topic examined peak expiratory flow rate (PEF) among school-aged children who previously participated in the aforementioned Finland PEACE study.(Pekkanen et al., 1997; Roemer et al., 1999; Tiittanen et al., 1999) Pekkanen et al., 1997 restricted their analysis to data from 39 children with asthma who lived in the center of town (capture area analysis). Investigators did not find significant associations between UFPs and PEF (measured in the morning and evening).(Pekkanen et al., 1997)

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Tiittanen et al., 1999 also collected UFP and PEF data on prior PEACE study participants. Like Pekkanen et al., 1997, this investigation found no significant associations between UFPs (≤0.01 μm) and PEF.(Tiittanen et al., 1999) However, the authors noted a significant inverse association between slightly larger particles (0.1–1 μm) and evening PEF (β = −1.6, standard error[SE] = 0.7, $P < .05$), and UFP number concentration correlated with these larger particles (Spearman $r = 0.39$, $P < .05$).(Tiittanen et al., 1999) No significant association between UFPs and morning PEF was observed.(Tiittanen et al., 1999) The temporal specificity of this relationship could be attributable to lower evening temperatures near the ground, which increase the ability of atmospheric layers to trap primary pollutants near their emissions source.(Herner et al., 2006; HEI, 2013)

Over a decade later, in 2009, Newcomb et al., 2012 published results from a pilot study examining the respiratory health effects of walking indoors versus outdoors among 24 U.S. children with asthma. In comparison to aforementioned literature, the racial/ethnic composition of this sample was more heterogeneous: >50% (13/24) of children were African American, and the remainder were Mexican American or non-Hispanic white.(Newcomb et al., 2012) Using a case-crossover design, investigators assessed UFP and PM_{10} exposure by carrying monitors behind groups of children as they walked indoors and outdoors on a university campus (children walked 30-minute intervals daily for 5 days indoors and for 5 days outdoors, with a 2-week washout period in between).(Newcomb et al., 2012) At the end of each 5-day period, researchers assessed children using spirometry (forced expiratory flow rate in 1 second [FEV_1], forced expiration between 25% and 75% of vital capacity [$FEF_{25–75}$]) and eNO. Although the authors found no significant associations directly relating UFP number concentration to respiratory outcomes (α = 0.1 in this pilot study), they reported that type of walking environment (indoor versus outdoor) significantly interacted with UFP number concentration in predicting $FEF_{25–75}$ (indoor environment β = 0.01, SE = 0.007, $P = .07$).(Newcomb et al., 2012)

Most recently, in 2013, Buonanno et al., 2013 published a study of how UFPs were related to eNO and spirometric outcomes among 103 Italian children. To assess exposure to UFPs (defined in their study as 0.01–0.3 μm in diameter), investigators used personal monitors worn by children for 2 days and calculated daily alveolar and tracheobronchial deposited surface area dose, which accounted for alveolar and tracheobronchial surface area concentration of inhaled particles, time in each microenvironment, activity, and inhalation rate during the activity.(Buonanno et al., 2012; Buonanno et al., 2013) This study was the first to determine a direct association between personal dose and respiratory health effects. (Buonanno et al., 2013) Investigators documented statistically significant negative correlations between UFP daily deposited surface area dose and spirometry (i.e., FEV_1 and $FEF_{25–75}$).(Buonanno et al., 2013) Notably, a 100 mm^2 dose increase of UFPs was associated with a 0.3% decrease in FEV_1 ($P = 0.02$) and a 0.8% decrease in $FEF_{25–75}$ ($P = 0.004$).(Buonanno et al., 2013)

In addition, Buonanno et al., 2013 reported a significant association between UFP dose and eNO in a subanalysis limited to the 16% of children in their sample who had asthma (β = 0.04, $P < .01$).(Buonanno et al., 2013) A similar relationship was found for children without asthma but with house dust mite (HDM) allergy (β = 0.04, $P < .01$), whom they identified

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through skin prick testing.(Buonanno et al., 2013) No significant association between UFP dose and eNO was found for the remaining 68% (70/103) of children without asthma or HDM allergy ($\beta = 0.02$, $P > .01$).(Buonanno et al., 2013) Results from Buonanno et al., 2013 add to the evidence for respiratory health effects of UFPs in children, although the effects specific to particles <0.1 μm could not be differentiated from those with diameters of 0.2–0.3 μm in this study. A strength of this study was the conservative threshold for statistical significance ($\alpha = 0.01$), especially given the multiple statistical testing performed. Adjusting for potential confounders (e.g., other pollutants) would have enhanced these findings further.

In summary, 4 studies have investigated the relationship between UFPs and objective measures of respiratory health (i.e., spirometry and eNO) in children. Early investigations did not reveal significant associations between UFPs and PEF, but study power might have been limited by sample size. Later work included use of more sophisticated exposure assessments (e.g., UFP dose estimations(Buonanno et al., 2013) and use of personal or mobile exposure monitors(Buonanno et al., 2013; Newcomb et al., 2012); decreased measurement error because of advances in exposure assessment could be responsible for the significant or stronger associations reported more recently.(Buonanno et al., 2013) Certain populations (e.g., children with respiratory symptoms, asthma, or HDM allergy) might be particularly susceptible to the respiratory health effects of UFPs(Buonanno et al., 2013; Tiittanen et al., 1999); specificity within subpopulations could be meaningful in understanding how significant findings might indicate true associations. However, the absence of effect estimates adjusted for other pollutants limits the strength of any conclusions that can be drawn from these data.(HEI, 2013) Thus, although some studies have identified significant relationships between UFPs and objective respiratory health measurements in children(Buonanno et al., 2013; Tiittanen et al., 1999), the existing literature as a whole is currently not strong enough to yield definitive answers.

3.6 Health Care Utilization Related to Respiratory Health

To date, five publications have investigated the relationship between UFPs and health care utilization related to respiratory health (Table 3). Two articles addressed hospitalizations(Andersen et al., 2008b; Iskandar et al., 2012), one examined emergency department (ED) visits(Halonen et al., 2008), another focused on outpatient visits(Diaz-Robles et al., 2014), and the fifth used a composite outcome of ED visits and acute outpatient visits(Evans et al., 2014).

3.6.1 Hospitalizations—Andersen et al., 2008b investigated the relationship between UFPs (<0.1 μm) and hospitalizations for asthma for children aged 5–18 years in Denmark from 2001–2004. The authors used national registry data to examine daily hospitalization counts for 9 Copenhagen hospitals within a 15 km radius of a central ambient monitor. (Andersen et al., 2008b) Asthma-related hospitalizations were defined as those with admission diagnoses containing the International Classification of Diseases, 10th Revision (ICD-10) codes J45 (asthma) or J46 (status asthmaticus).(Andersen et al., 2008b; WHO, 2015) In their analyses, investigators reviewed 1,327 days of data and controlled for overdispersion (i.e., data variability in excess of their model's typical assumptions), season, day of the week, holidays, and weather.(Andersen et al., 2008b; Wu et al., 2015) They did

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not find UFPs to be significantly associated with asthma-related hospitalizations (OR [95% CI] = 1.06 [0.97–1.16]).(Andersen et al., 2008b) However, the study was limited in power because of relatively few daily pediatric asthma-related hospitalizations in Copenhagen (mean of 3 admissions per day).(Andersen et al., 2008b)

Several years later, investigators examined asthma-related hospitalizations in Copenhagen over a longer period of time (2001–2008) and for a wider age range of children (0–18 years). (Iskandar et al., 2012) This study's hospital data and variable measurement were similar to Andersen et al., 2008b, but the analytical methodology differed: while Andersen et al., 2008b used a time series Poisson generalized additive model and adjusted for various confounders, this subsequent study addressed confounding by employing a case crossover design (i.e., children served as their own controls).(Iskandar et al., 2012) Nevertheless, these investigators also found a weak positive but non-significant association between UFPs and pediatric asthma-related hospitalizations (OR [95% CI] = 1.06 [0.98–1.14], $P = .14$). (Iskandar et al., 2012) Stratified results by sex and age group revealed similar non-significant results. (Iskandar et al., 2012)

3.6.2 Emergency Department and Outpatient Visits—Halonen et al., 2008 investigated the relationship between UFPs (0.03–0.1 μm; measured from a central monitoring site) and asthma-related ED visits for children aged <15 years at 3 hospitals in the Helsinki metropolitan area of Finland from 1998–2004. Asthma-related ED visits were identified using ICD-10 codes.(Halonen et al., 2008; WHO, 2015) The authors found that interquartile (IQR) increases in UFP number concentration were significantly associated with asthma-related ED visits at 3–5 day lags ($P < .05$), even after adjusting for day of the week, holidays, influenza, pollen, and weather.(Halonen et al., 2008) Beyond single-pollutant models, the authors assessed the potential role of co-pollutants using two-pollutant models. They found that the relationship between UFPs and asthma-related ED visits (4-day lag) was no longer significant after accounting for nitrogen dioxide (NO_2).(Halonen et al., 2008)

A subsequent study, the first to originate in Latin America, was the first to examine the relationship between UFPs and outpatient visits related to respiratory health in children. (Diaz-Robles et al., 2014) Diaz-Robles et al., 2014 analyzed associations between UFPs (≤0.1 μm) and outpatient visits for respiratory health at 3 municipal health care centers for children aged 0–5 years in Temuco City, Chile. Investigators obtained UFP data (2009–2011) from a central monitoring site and said they considered illnesses beginning with the letter “J” (i.e., J00–J99) in the ICD-10 when classifying outpatient visit data.(Diaz-Robles et al., 2014; WHO, 2015) They identified 14,232 visits classified as “respiratory” and 9,526 classified as “other respiratory health”; further details about visit adjudication were limited. The risk ratio for an IQR increase (4.73 $\mu g/m^3$) in UFPs for “other respiratory health” visits was 1.05 (95% CI = 1.00–1.11, $P < .001$). No other findings were statistically significant for these young children ($P > .05$). These authors combined data for children aged 6–17 years with data for adults aged 18–64 years.(Diaz-Robles et al., 2014) We could not derive child-specific estimates from published estimates for persons aged 6–64 years.

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Finally, Evans et al., 2014 examined the relationship between UFPs (<0.1 μm) and asthma-related ED or outpatient visits (i.e., a composite outcome) among 74 children aged 3–10 years with asthma who participated in the School-Based Asthma Therapy Trial in Rochester, New York.(Evans et al., 2014) Children were recruited from >60 schools in one school district, and investigators verified asthma diagnoses through children's primary care physicians.(Evans et al., 2014) Of participating children, 65% were African American and 32% were Hispanic.(Evans et al., 2014) UFP data were obtained from a central monitor. (Evans et al., 2014) Acute pediatric asthma visits were defined as doctor's office or ED visits where prednisone was prescribed for asthma; this information was assessed through monthly study phone interviews with children's caregivers.(Evans et al., 2014) A total of 96 acute pediatric asthma visits were reported, representing 74 children.(Evans et al., 2014) Using a case-crossover study design, investigators analyzed relationships between acute pediatric asthma visits and UFP number concentration, while adjusting for temperature and relative humidity.(Evans et al., 2014) Increases in acute pediatric asthma visits appeared to parallel IQR increases in UFP concentrations; the largest increase was observed for the 4-day average of UFPs (IQR = 2088 p/cm^3; OR [95% CI] =1.27 [0.90–1.79], P = .17).(Evans et al., 2014) No statistically significant effects were identified, but the small sample size might have limited study power.(Evans et al., 2014) Separate estimates for outpatient visits and ED visits were not reported.(Evans et al., 2014)

4. Discussion

In our review of literature on the respiratory health effects of UFPs in children, we identified 12 published studies. Half were conducted in Scandinavia, and most (8/12) used 0.1 μm to define UFPs. An equal percentage of studies analyzed outdoor UFP measurements from central monitoring sites. UFPs were significantly associated with incident wheezing among Danish infants(Andersen et al., 2008a), current asthma among Korean schoolchildren(Kim et al., 2011), objective lung findings (spirometry and eNO) in studies from Italy and the United States(Buonanno et al., 2013; Newcomb et al., 2012), asthma-related ED visits in Finland(Halonen et al., 2008), and certain respiratory outpatient visits in Chile.(Diaz-Robles et al., 2014) We found that interpretation of statistically significant associations was limited by frequent reliance on outdoor central monitoring data(Andersen et al., 2008a; Diaz-Robles et al., 2014; Halonen et al., 2008), which did not account for the known spatial variability of UFPs (distance and indoor/outdoor environments) and could thus result in exposure misclassification.(Andersen et al., 2008b; HEI, 2013) Furthermore, among studies reporting significant findings, only 1 examined potential confounding by other air pollutants.(Halonen et al., 2008) These investigators determined the relationship between UFPs and asthma-related pediatric ED visits was no longer significant after adjusting for NO_2.(Halonen et al., 2008)

Despite concerns that UFPs might be responsible for the documented adverse health effects of $PM_{2.5}$ and PM_{10}(HEI, 2013; Terzano et al., 2010), studies addressing this question are few for both pediatric and adult populations.(EPA, 2009; HEI, 2013) Some chamber exposure experiments involving adults have revealed associations between UFPs, arterial oxygen saturation, and spirometric measures.(Gong et al., 2009; HEI, 2013; Pietropaoli et al., 2004) A few epidemiologic studies have reported UFP effects on lung function and

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airway inflammation among adults, particularly those with asthma.(McCreanor et al., 2007; HEI, 2013; Zhang et al., 2009) Two of the articles discussed in this review included sub-analyses of adult populations, which found that UFPs were related to hospital admissions and ED visits for respiratory diseases.(Andersen et al., 2008b; Halonen et al., 2008) UFPs and respiratory mortality have also been linked using adult data.(HEI, 2013; Wichmann et al., 2000) Similar to the pediatric literature, interpretation of UFP data from adults is constrained by heterogeneity in defining UFPs, frequent reliance on central monitors, and inconsistency in addressing confounding effects by other pollutants.(HEI, 2013)

Since the most recent comprehensive summary of UFP health effects in 2013(HEI, 2013), the number of studies investigating UFPs and children's respiratory health increased by 50%.(Buonanno et al., 2013; Diaz-Robles et al., 2014; Evans et al., 2014; Spickett et al., 2014) Of these latest additions to the literature, most (75%) reported significant findings. We reviewed these articles and discussed how they complement prior literature. Notably, advances in measuring exposure and objective respiratory health outcomes have been associated with reports of stronger associations between UFPs and respiratory health. (Buonanno et al., 2013) Also, recent studies advanced understanding of potential UFP sources across different indoor microenvironments of children; these data could be useful for developing strategies to reduce or mitigate UFP exposure among children.(Buonanno et al., 2012; Buonanno et al., 2013) Our findings highlight opportunities to improve understanding of potential UFP effects on this vulnerable population, which could in turn inform public health. For example, the 2 studies in our review that examined UFPs in children's homes identified potentially modifiable environmental factors (e.g., pets or fireplaces in the home) that could lower UFP exposure in the setting where children spend the majority of their day (i.e., at home).(IOM, 2000; Buonanno et al., 2013; Spickett et al., 2014) Moreover, the finding of high UFP exposure during cooking or eating(Buonanno et al., 2013) suggests that kitchen ventilation or cooking practices might be worthy targets for public health strategies, if a definitive relationship between UFPs and respiratory health is established in the future.

Increased uniformity in defining UFPs, more frequent use of personal UFP measurements, and more widespread use of multi-pollutant models could make the current literature on respiratory health effects of UFPs in children more conclusive. Larger sample sizes would enhance confidence in non-significant findings. Other approaches to advance this field include replicating positive findings in diverse populations, describing UFP sources, distinguishing between indoor and outdoor UFPs, and utilizing land use regression models to assess relationships between UFP exposure and respiratory health.(Patton, 2015) Lastly, research on the long-term or cumulative dose effects of UFPs on the respiratory health of children would be novel.

Our review had several limitations. Publication bias might have caused positive findings to be overrepresented in the literature. Because of heterogeneity in outcome reporting, we could not calculate summary effect estimates. We do not have access to data from ongoing studies.(Ezz et al., 2015) Our ability to review potential differences in UFP composition and adsorbed chemicals was limited by the availability of this information in the literature. Also,

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our methods did not account for the possibility that observed health effects might be attributable to UFP exposure in utero.(Peterson et al., 2015)

5. Conclusions

In our review of the current literature on UFPs and respiratory health effects among children, we found that evidence for a relationship has continued to increase but is not yet conclusive. Interpretation of existing data is constrained by heterogeneous UFP definitions, varied study designs, limited use of personal UFP monitors and multi-pollutant modeling, and lack of long-term follow-up. Addressing these challenges could increase understanding of how UFPs might affect this vulnerable population and might reveal worthy opportunities for public health intervention.

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References

Andersen ZJ, et al. Ambient air pollution triggers wheezing symptoms in infants. Thorax. 2008a; 63:710–6. [PubMed: 18267985]

Andersen ZJ, et al. Size distribution and total number concentration of ultrafine and accumulation mode particles and hospital admissions in children and the elderly in Copenhagen, Denmark. Occup Environ Med. 2008b; 65:458–66. [PubMed: 17989204]

Boehmer TK, et al. Residential proximity to major highways - United States, 2010. MMWR Surveill Summ. 2013; 62(Suppl 3):46–50. [PubMed: 24264489]

Boothe VL, et al. Residential traffic exposure and childhood leukemia: a systematic review and meta-analysis. Am J Prev Med. 2014; 46:413–22. [PubMed: 24650845]

Bowatte G, et al. The influence of childhood traffic related air pollution exposure on asthma, allergy and sensitization: a systematic review and a meta-analysis of birth cohort studies. Allergy. 2014

Buonanno G, et al. Individual dose and exposure of Italian children to ultrafine particles. Sci Total Environ. 2012; 438:271–7. [PubMed: 23000716]

Buonanno G, et al. Health effects of daily airborne particle dose in children: direct association between personal dose and respiratory health effects. Environ Pollut. 2013; 180:246–50. [PubMed: 23792384]

Chung Y, et al. Associations between long-term exposure to chemical constituents of fine particulate matter (PM2.5) and mortality in Medicare enrollees in the eastern United States. Environ Health Perspect. 2015; 123:467–74. [PubMed: 25565179]

Diapouli E, et al. Indoor and outdoor PM mass and number concentrations at schools in the Athens area. Environ Monit Assess. 2008; 136:13–20. [PubMed: 17458512]

Diaz-Robles LA, et al. Health risks caused by short term exposure to ultrafine particles generated by residential wood combustion: a case study of Temuco, Chile. Environ Int. 2014; 66:174–81. [PubMed: 24607502]

Evans KA, et al. Increased ultrafine particles and carbon monoxide concentrations are associated with asthma exacerbation among urban children. Environ Res. 2014; 129:11–9. [PubMed: 24528997]

Ezz WN, et al. Ultrafine Particles from Traffic Emissions and Children's Health (UPTECH) in Brisbane, Queensland (Australia): study design and implementation. Int J Environ Res Public Health. 2015; 12:1687–702. [PubMed: 25648226]

Gauderman WJ, et al. Association of improved air quality with lung development in children. N Engl J Med. 2015; 372:905–913. [PubMed: 25738666]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Gong L, et al. Ultrafine particles deposition inside passenger vehicles. Aerosol Sci Technol. 2009; 43:544–553.

Halonen JI, et al. Urban air pollution, and asthma and COPD hospital emergency room visits. Thorax. 2008; 63:635–41. [PubMed: 18267984]

HEI Review Panel on Ultrafine Particles. HEI Perspectives 3. Health Effects Institute; Boston, MA: 2013. Understanding the health effects of ambient ultrafine particles.

Herner J, et al. Dominant mechanisms that shape the airborne particle size and composition distribution in central California. Aerosol Sci Technol. 2006; 40:827–844.

Institute of Medicine (US) Committee on the Assessment of Asthma and Indoor Air. Clearing the air: asthma and indoor air exposures. National Academies Press (US); Washington (DC): 2000.

Iskandar A, et al. Coarse and fine particles but not ultrafine particles in urban air trigger hospital admission for asthma in children. Thorax. 2012; 67:252–7. [PubMed: 22156960]

Karner AA, et al. Near-roadway air quality: synthesizing the findings from real-world data. Environ Sci Technol. 2010; 44:5334–44. [PubMed: 20560612]

Kim JL, et al. Respiratory health among Korean pupils in relation to home, school and outdoor environment. J Korean Med Sci. 2011; 26:166–73. [PubMed: 21286005]

Kreyling WG, et al. Ultrafine particle-lung interactions: does size matter? J Aerosol Med. 2006; 19:74–83. [PubMed: 16551218]

Laumbach RJ, Kipen HM. Respiratory health effects of air pollution: update on biomass smoke and traffic pollution. J Allergy Clin Immunol. 2012; 129:3–11. quiz 12–3. [PubMed: 22196520]

McCreanor J, et al. Respiratory effects of exposure to diesel traffic in persons with asthma. N Engl J Med. 2007; 357:2348–58. [PubMed: 18057337]

Nazaroff WW. Indoor particle dynamics. Indoor Air. 2004; 14(Suppl 7):175–83. [PubMed: 15330785]

Newcomb P, et al. Acute effects of walking environment and GSTM1 variants in children with asthma. Biol Res Nurs. 2012; 14:55–64. [PubMed: 21196426]

Ostro B, et al. Associations of mortality with long-term exposures to fine and ultrafine particles, species and sources: results from the California Teachers Study Cohort. Environ Health Perspect. 2015; 123:549–56. [PubMed: 25633926]

Patton AP, et al. Transferability and generalizability of regression models of ultrafine particles in urban neighborhoods in the Boston area. Environ Sci Technol. 2015; 19:6051–60. [PubMed: 25867675]

Pekkanen J, Kulmala M. Exposure assessment of ultrafine particles in epidemiologic time-series studies. Scand J Work Environ Health. 2004; 30(Suppl 2):9–18. [PubMed: 15487681]

Pekkanen J, et al. Effects of ultrafine and fine particles in urban air on peak expiratory flow among children with asthmatic symptoms. Environ Res. 1997; 74:24–33. [PubMed: 9339211]

Peterson BS, et al. Effects of prenatal exposure to air pollutants (polycyclic aromatic hydrocarbons) on the development of brain white matter, cognition, and behavior in later childhood. JAMA Psychiatry. 2015

Pietropaoli AP, et al. Pulmonary function, diffusing capacity, and inflammation in healthy and asthmatic subjects exposed to ultrafine particles. Inhal Toxicol. 2004; 16(Suppl 1):59–72. [PubMed: 15204794]

Polidori A, et al. Pilot study of high-performance air filtration for classroom applications. Indoor Air. 2013; 23:185–95. [PubMed: 23137181]

Pope CA 3rd, Dockery DW. Health effects of fine particulate air pollution: lines that connect. J Air Waste Manag Assoc. 2006; 56:709–42. [PubMed: 16805397]

Roemer W, et al. Inhomogeneity in response to air pollution in European children (PEACE project). Occup Environ Med. 1999; 56:86–92. [PubMed: 10448312]

Schuepp K, Sly PD. The developing respiratory tract and its specific needs in regard to ultrafine particulate matter exposure. Paediatr Respir Rev. 2012; 13:95–9. [PubMed: 22475255]

Spickett J, et al. The domestic environment and respiratory health of school children in Zongshan, China. Asia Pac J Public Health. 2014; 26:596–603. [PubMed: 23355054]

Terzano C, et al. Air pollution ultrafine particles: toxicity beyond the lung. Eur Rev Med Pharmacol Sci. 2010; 14:809–21. [PubMed: 21222367]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Tiittanen P, et al. Fine particulate air pollution, resuspended road dust and respiratory health among symptomatic children. Eur Respir J. 1999; 13:266–73. [PubMed: 10065666]

U. S. Environmental Protection Agency. 2009 Final report: integrated science assessment for particulate matter. U. S. Environmental Protection Agency; Washington, DC: 2009. EPA/600/R-08/139F

[Accessed 2 March 2015] U. S. Environmental Protection Agency National Ambient Air Quality Standards. http://www.epa.gov/air/criteria.html

Weichenthal S, et al. Characterizing and predicting ultrafine particle counts in Canadian classrooms during the winter months: model development and evaluation. Environ Res. 2008; 106:349–60. [PubMed: 17919560]

World Health Organization. [Accessed 1 May 2015] International Classification of Diseases. http://www.who.int/classifications/icd/en/

Wichmann HE, et al. Daily mortality and fine and ultrafine particles in Erfurt, Germany part I: role of particle number and particle mass. Res Rep Health Eff Inst. 2000:5–86. discussion 87–94. [PubMed: 11918089]

Wu W, et al. A Bayesian approach to account for misclassification and overdispersion in count data. Int J Environ Res Public Health. 2015; 28:10648–61. [PubMed: 26343704]

Zhang JJ, et al. Health effects of real-world exposure to diesel exhaust in persons with asthma. Res Rep Health Eff Inst. 2009:5–109. discussion 111–23. [PubMed: 19449765]

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Table 1

Epidemiologic Studies Examining Ultrafine Particles and Subjective Respiratory Outcomes Among Children

Author (Year)	Study Setting; Design; Population	UFP Definition (Measure[a])	Other Measured Pollutants[b]	Source of Outcome Measure	Results[b]
Tiitanen et al. (1999)	Finland 1995; longitudinal study; 49 children aged 8–13 years with chronic respiratory symptoms[c]	0.01–0.1 μm (central ambient monitor, electric aerosol spectrometer)	Black carbon, CO, NO_2, O_3, particles 0.1–1 μm, $PM_{2.5}$, PM_{10}, SO_2, total suspended particles	Child diary	Bronchodilator use increased during days with UFP levels in the highest tertile, but the association was not statistically significant No statistically significant associations reported for UFPs (lags 0–3 and 4-day average) and other outcomes assessed (cough, phlegm, other respiratory symptoms, asthma controller medication[d])
Andersen et al. (2008)	Denmark 1998–2004; birth cohort; 205 children aged 0–3 years at high risk for wheeze[e]	0.01–0.7 μm[f] (central ambient monitor, Differential Mobility Particle Sizer, Roskilde, Denmark)	CO, NO_2, NO_x, O_3, $PM_{2.5}$, PM_{10}	Parent diary	UFPs (3-day average) and incident wheeze among children living ≤5 km from particle monitor: 0–1 years: OR (95% CI) = 2.5 (1.0–5.8)[g] 1–2 years: OR (95% CI) = 1.1 (0.6–1.9)[g] 2–3 years: OR (95% CI) = 0.4 (0.2–0.8)[g] No statistically significant association reported for UFPs (lags 0–4 and 3-day average) and incident wheeze among the entire sample
Kim et al. (2011)	South Korea 2004; cross-sectional school-based study; 2,400 4th grade students (mean age, 10 years)	0.02–1 μm (indoor and outdoor air sampling at schools, PTrak™ model 8525, TSI Inc.)	CO_2, formaldehyde, NO_2, SO_2, O_3	Child questionnaire	Outdoor UFPs and current asthma[h]: OR (95% CI) = 1.93 (1.08–3.46) No statistically significant associations reported for outdoor UFPs and physician-diagnosed asthma or recent wheeze

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Author (Year)	Study Setting; Design; Population	UFP Definition (Measure[a])	Other Measured Pollutants[b]	Source of Outcome Measure	Results[b]
					No statistically significant associations reported for indoor UFPs and any outcomes assessed (physician-diagnosed asthma or symptoms in the past 12 months)
Spickett et al. (2014)	China 2006–2007; cross-sectional school-based study; 37 children aged 9–13 years[i]	<0.1 μm (indoor and outdoor home air sampling[j], PTrak™, TSI Inc.)	None	Parent questionnaire	No statistically significant associations reported for UFPs and any outcomes assessed (various respiratory symptoms in the past several months or prior history of asthma, chronic bronchitis, or emphysema)

CI, confidence interval; CO, carbon monoxide; CO_2, carbon dioxide; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; O_3, ozone; OR, odds ratio; $PM_{2.5}$, particulate matter ≤2.5 μm; PM_{10}, particulate matter ≤10 μm; SO_2, sulfur dioxide; UFP, ultrafine particle.

[a] UFP exposure was measured using particle number concentration.

[b] No statistically significant associations between UFPs and respiratory health outcomes were obtained from models that controlled for other pollutants.

[c] Study inclusion criteria included parent report of ≥1 of the following: recent wheeze (apart from colds), recent attacks of shortness of breath with wheezing, recent dry cough (apart from colds), or asthma ever diagnosed by a doctor.

[d] Defined as inhaled corticosteroids, sodium cromoglycate, or nedocromil.

[e] Children's mothers reported receiving a physician's diagnosis of asthma after age 7 years and having a history of daily treatment with inhaled β agonists or glucocorticoids.

[f] Study investigators reported that >95% of these total concentration measurements were <0.1 μm.

[g] Adjusted for age, gender, exposure to smoking, paternal asthma history, temperature, and season.

[h] Defined as current asthma medication use or asthma attacks during the last 12 months and reported by 7% of students.

[i] The entire study sample was 359 children (asthma prevalence: 6%), and 37 of these children were chosen to receive UFP exposure measurements. Investigators considered these 37 homes (32 apartments and 5 houses) representative of 3 different residential areas, according to levels of traffic and distance to the central business district.

[j] Indoor air samples were taken from children's bedrooms, living rooms, and kitchens. Outdoor samples were taken from the doorway or balcony of children's homes.

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Table 2

Epidemiologic Studies Examining Ultrafine Particles and Objective Respiratory Outcomes Among Children

Author (Year)	Study Setting; Design; Population	UFP Definition (Measure)	Other Measured Pollutants[b]	Source of Outcome Measure	Results[b]
Pekkanen et al. (1997)	Finland 1994; longitudinal study; 39 children aged 7–12 years with asthma[c]	0.01–0.032 μm, 0.032–0.1 μm (central ambient monitor, electric aerosol spectrometer)	Black smoke, CO, NO, NO_2, O_3, particles 0.1–10 μm, $PM_{2.5}$, PM_{10}, SO_2	PEF (morning, evening)	No statistically significant associations reported for UFPs (lags 0–3 and 4-day average) and any PEF
Tiitanen et al. (1999)	Finland 1995; longitudinal study; 49 children aged 8–13 years with chronic respiratory symptoms[d]	0.01–0.1 μm (central ambient monitor, electric aerosol spectrometer)	Black carbon, CO, NO_2, O_3, particles 0.1–1 μm, $PM_{2.5}$, PM_{10}, SO_2, total suspended particles	PEF (morning, evening)	Evening PEF (1-day lag): β = −1.00, SE = 0.60, $P < .10$ No statistically significant association reported for UFPs (lags 0–3 and 4-day average) and morning PEF
Newcomb et al. (2012)	United States 2009; case-crossover study; 24 children aged 5–12 years with asthma[e]	0.02–1 μm (indoor and outdoor air sampling near children[f], PTrak™, TSI Inc.)	PM_{10}	eNO, FEV_1, $FEF_{25–75}$	No statistically significant associations reported for UFPs and any outcomes assessed[g]
Buonanno et al. (2013)	Italy 2010–2011; cross-sectional study; 103 children aged 8–11 years[h]	0.01–0.3 μm (personal 2-day monitor, NanoTracer, Philips)	None	eNO, $FEF_{25–75}$	UFP dose[i] and FEV_1: β = −0.003, SD = 0.001, $P = 0.02$ UFP dose[i] and $FEF_{25–75}$: β = −0.008, SD = 0.003, $P = 0.004$ UFP dose[i] and eNO among children with asthma or HDM allergy[j]: β = 0.04, $P < .01$

CO, carbon monoxide; eNO, exhaled nitric oxide; $FEF_{25–75}$, forced expiration between 25% and 75% of vital capacity; FEV_1, forced expiratory flow rate in 1 second; HDM, house dust mite; NO, nitric oxide; NO_2, nitrogen dioxide; O_3, ozone; PEF, peak expiratory flow rate; $PM_{2.5}$, particulate matter ≤2.5 μm; PM_{10}, particulate matter ≤10 μm; SD, standard deviation, SE, standard error; SO_2, sulfur dioxide; UFP, ultrafine particle.

[a] UFP exposure was measured using particle number concentration in all studies except Buonanno et al., which calculated daily alveolar and tracheobronchial deposited surface area dose.

[b] No statistically significant associations between UFPs and respiratory health outcomes were obtained from models that controlled for other pollutants.

[c] Defined as physician-diagnosed asthma or reported wheezing or "attacks of shortness of breath with wheezing" during the previous 12 months. Although Pekkanen et al., 1997 studied children from the same study population as Tiitanen et al., 1999, the earlier study restricted their analysis to data from children who "lived in the center of town" and completed >60% of their self-reported PEF daily diary.

[d] At least 1 of the following (by parent report): recent wheeze or dry cough (apart from colds), recent attacks of shortness of breath with wheezing, or asthma ever diagnosed by a doctor.

[e] Physician-diagnosed.

[f] Investigators carried particle counters behind groups of study participants at the time of the study intervention (i.e., walking indoors or outdoors within the university where the study was conducted. Investigators reported that most children lived in the same neighborhood as this university.

[g] Although the authors found no significant associations directly relating UFPs to respiratory outcomes ($\alpha = 0.1$ in this pilot study), they reported that type of walking environment (indoor versus outdoor) significantly interacted with UFP number concentration in predicting $FEF_{25–75}$ (indoor environment $\beta = 0.01$, SE = 0.007, $P = .07$). Lag structure was not reported.

[h] Asthma prevalence in this sample was 16%.

[i] Calculated daily alveolar and tracheobronchial deposited surface area dose, which accounted for alveolar and tracheobronchial surface area concentration of inhaled particles, time in each microenvironment, activity, and inhalation rate during each activity.

[j] Assessed by skin prick testing.

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Table 3

Epidemiologic Studies Examining Ultrafine Particles and Health Care Utilization Related to Respiratory Health Among Children

Author (Year)	Study Setting; Design; Population	UFP Definition (Measure[a])	Other Measured Pollutants[b]	Source of Outcome Measure	Results[b]
Andersen et al. (2008)	Denmark 2001–2004; time series; 1,327 days of hospitalization counts for children aged 5–18 years from 9 hospitals	<0.1 μm (central ambient monitor, Differential Mobility Particle Sizer, Roskilde, Denmark)	CO, NO_2, NO_x, O_3, $PM_{2.5}$, PM_{10}	Asthma-related hospitalizations, identified using ICD-10 codes[c]	UFPs (5-day average of lags 0–4) and asthma-related hospitalizations: OR (95% CI) = 1.06 (0.97–1.16)[d]
Halonen et al. (2008)	Finland 1998–2004; time series; 2,557 days of ED visit counts for children aged <15 years from 3 hospitals	<0.03 μm, 0.03–0.1 μm (central ambient monitor, Differential Mobility Particle Sizer, University of Helsinki)	CO, NO_2, O_3, particles 0.1–0.29 μm, $PM_{2.5}$, PM_{10}	Asthma-related ED visits, identified using ICD-10 codes[c]	UFPs (0.03–0.1 μm) and % increase in asthma-related ED visits[e]: (3-day lag) 4.5% (95% CI = 1.5–7.6%) (4-day lag) 6.0% (95% CI = 3.1–9.1%) (5-day lag) 5.2% (95% CI = 2.3–8.1%)
Iskandar et al. (2012)	Denmark 2001–2008; case-crossover; 1,653 days of hospitalization counts for children aged 0–18 years from 8 hospitals	0.01–0.7 μm[f] (central ambient monitor, Differential Mobility Particle Sizer, Roskilde, Denmark)	NO_2, NO_x, $PM_{2.5}$, PM_{10}	Asthma-related hospitalizations, identified using ICD-10 codes[c]	UFPs (5-day average of lags 0–4) and asthma-related hospitalizations: OR (95% CI) = 1.06 (0.98–1.14)
Diaz-Robles et al. (2014)	Chile 2009–2011; time series; 679 days of outpatient visit counts for children aged 0–4 years from 3 municipal health care centers	≤0.1 μm (central ambient monitor, Micro-Orifice Uniform-Deposit Impactor, 100-NR model, MSP Corporation)	None	Outpatient visits for respiratory health or "other respiratory" causes[g]	UFPs (lag 4) and outpatient visits for "other respiratory" causes[g]: RR (95% CI) = 1.05 (1.00–1.11) No statistically significant associations reported for UFPs (5-day average of lags 1–5) and other outcomes
Evans et al. (2014)	United States 2006–2008; case-crossover; 74 children aged 3–10 years with physician-diagnosed persistent asthma	<0.1 μm (central ambient monitor, Scanning Mobility Particle Sizer, TSI Inc.)	Black carbon, CO, O_3, particles 0.1–0.5 μm, $PM_{2.5}$, SO_2	Acute pediatric asthma visits[h]	No statistically significant associations reported for UFPs (1–7 day averages) and outcome

CO, carbon monoxide; CI, confidence interval; ED, Emergency Department; ICD-10, International Classification of Diseases, 10th Revision; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; O_3, ozone; OR, odds ratio; $PM_{2.5}$, particulate matter ≤2.5μm; PM_{10}, particulate matter ≤10 μm; RR, relative risk; SO_2, sulfur dioxide; UFP, ultrafine particle.

[a] UFP exposure was measured using particle number concentration.

[b] No statistically significant associations between UFPs and respiratory health outcomes were obtained from models that controlled for other pollutants.

[c] J45 (asthma) or J46 (status asthmaticus).

[d] Adjusted for overdispersion, season, day of the week, holidays, influenza, pollen, and weather.

[e] Per interquartile increase in number concentration of UFPs 0.03–0.1 μm in diameter, adjusted for day of the week, holidays, influenza, pollen, and weather.

[f] Study investigators reported that >75% of these total concentration measurements were <0.1 μm.

[g] Per interquartile increase in UFP number concentration (4-day lag). The authors stated that ICD-10 codes beginning with the letter “J” (i.e., J00–J99) were considered when they classified outpatient visits, but further definitions were not available in the text.

[h] Defined as any physician outpatient visit or ED visit where prednisone was prescribed (as reported by children's caregivers).

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