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Ambient air pollution epidemiology systematic review and meta-analysis: A review of reporting and methods practice

Mary C. Sheehan [a], Juleen Lam [b,*], Ana Navas-Acien [c], Howard H. Chang [d]

[a] Department of Health Policy & Management, Johns Hopkins Bloomberg School of Public Health, United States
[b] Program on Reproductive Health and the Environment, Department of OB/GYN & RS, University of California, San Francisco, United States
[c] Environmental Health Sciences Department, Johns Hopkins Bloomberg School of Public Health, United States
[d] Department of Biostatistics and Bioinformatics, Emory University, United States

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ABSTRACT

Background: Systematic review and meta-analysis (SRMA) are increasingly employed in environmental health (EH) epidemiology and, provided methods and reporting are sound, contribute to translating science evidence to policy. Ambient air pollution (AAP) is both among the leading environmental causes of mortality and morbidity worldwide, and of growing policy relevance due to health co-benefits associated with greenhouse gas emissions reductions.

Objectives: We reviewed the published AAP SRMA literature (2009 to mid-2015), and evaluated the consistency of methods, reporting and evidence evaluation using a 22-point questionnaire developed from available best-practice consensus guidelines and emerging recommendations for EH. Our goal was to contribute to enhancing the utility of AAP SRMAs to EH policy.

Results and discussion: We identified 43 studies that used both SR and MA techniques to examine associations between the AAPs $PM_{2.5}$, PM_{10}, NO_2, SO_2, CO and O_3, and various health outcomes. On average AAP SRMAs partially or thoroughly addressed 16 of 22 questions (range 10–21), and thoroughly addressed 13 of 22 (range 5–19). We found evidence of an improving trend over the period. However, we observed some weaknesses, particularly infrequent formal reviews of underlying study quality and risk-of-bias that correlated with lower frequency of thorough evaluation for key study quality parameters. Several other areas for enhanced reporting are highlighted.

Conclusions: The AAP SRMA literature, in particular more recent studies, indicate broad concordance with current and emerging best practice guidance. Development of an EH-specific SRMA consensus statement including a risk-of-bias evaluation tool, would be a contribution to enhanced reliability and robustness as well as policy utility.

1. Introduction

The last decade has seen a marked increase in the use of systematic review and meta-analysis (SRMA) techniques in environmental health (EH) epidemiology. SRMA provides a transparent, thorough and replicable examination of available evidence that can offset the challenges of small sample size, identify and account for bias, demonstrate where effects are consistent across studies and generalizable across populations, and highlight research gaps (Woodruff and Sutton, 2014). Provided methods used are sound, this makes SRMA a valuable tool for translating a body of science findings into recommendations for health-protective decision- and policy-making (Moher et al., 2012), through contribution to health impact assessments, burden of disease estimates, cost-benefit analysis and other approaches. Use of SRMA in EH is relatively recent compared to other fields such as clinical medicine that have refined these methods over several decades, including through the Cochrane Collaboration (Higgins and Green, 2008). This is due in part to the typical EH evidence base which – given the difficulty of conducting randomized controlled trials for environmental contaminants in human populations – is reliant on observational studies that present a number of methodological challenges to pooling findings (Dickersin, 2002). These include inability to fully control for confounders, inconsistencies across studies in exposure metrics, and differences in outcomes, populations and study designs (Woodruff and Sutton, 2011; Rooney et al., 2014).

In the mid-1990s an expert group defined recommendations for use of SRMA that addressed many of the specificities of EH observational epidemiology (Blair et al. 1995), although these were not widely adopted as a formal guideline. While no specific consensus statement for use of SRMA in EH epidemiology is currently available, the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Statement

* Corresponding author.
E-mail addresses: msheeh10@jhu.edu (M.C. Sheehan), juleen.lam@ucsf.edu (J. Lam), anavas1@jhu.edu (A. Navas-Acien), howard.chang@emory.edu (H.H. Chang).

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(Moher et al., 2009) and the MOOSE (Meta-Analysis of Observational Studies in Epidemiology) Statement (Stroup et al., 2000) provide a basis for best-practice guidance. More recently, several inter-related efforts have brought about development, piloting and implementation of updated EH-specific SRMA methods. These include initiatives by the US Environmental Protection Agency (EPA) under its Integrated Risk Information System (IRIS) program (NRC 2011; NRC 2014; US EPA, 2014); by the US National Institutes of Environmental Health Sciences (NIEHS) National Toxicology Program (NTP) for its chemical assessments (Rooney et al., 2014); and by the Navigation Guide group, an interdisciplinary collaboration between academicians, practitioners, and clinicians (Woodruff and Sutton, 2011; Lam et al., 2014; Vesterinen et al. 2015) designed to improve the reliability and robustness of EH SRMAs, by incorporating risk-of-bias analysis and evaluation of strength-of-evidence.

Reviews of reporting and methods used in SRMAs have been published in several fields where the techniques are used as a means of comparing with best-practice, identifying strengths and areas for further development with a goal of enhancing the robustness and policy-utility of SRMAs (McElvenny et al. 2004; Brugha et al., 2012; Sheehan and Lam, 2015). As an example, the PRISMA statement evolved as a result of several sequential reviews of the quality of methods and reporting in the clinical medicine SRMA literature (Sacks et al. 1996; Moher et al. 1999). We had previously reviewed the methods and reporting used in 48 EH epidemiology SRMAs published over the period 1990 to mid-2013 and found a high degree of concordance with PRISMA and MOOSE guidelines and the Blair et al. (1995) recommendations; however, we also identified a number of gaps (in particular inconsistent SRMA reporting on use of exposure metrics and their comparability in underlying studies) and highlighted the need for development of EH-specific consensus SRMA guidelines (Sheehan and Lam, 2015).

Air pollution is the world's largest environmental health risk, accounting 1 in 8 deaths worldwide in 2012 (WHO, 2015a), with nearly half of the burden due to ambient, or outdoor air pollution (AAP; WHO, 2014). AAP is now also considered a leading environmental cause of lung cancer (IARC, 2013). AAP is commonly defined to include particulate matter of aerodynamic diameter <2.5 μm ($PM_{2.5}$) or <10 μm (PM_{10}), as well as carbon monoxide (CO), ground-level ozone (O_3), nitrogen dioxide (NO_2), and sulfur dioxide (SO_2). Human respiratory, cardiovascular and other health impacts of AAP have been extensively examined in epidemiological studies, and synthesized through use of SRMA, with a large number of reviews published in recent years (Cohen et al. 2005; WHO, 2014). Based in part on the AAP SRMA evidence base, the cost of AAP-related mortality and morbidity in Europe alone is estimated to exceed $1.5 trillion (WHO, 2015b).

AAP has also recently received increased policy attention because of its link to climate change. AAPs are largely emitted through burning of fossil fuels, a process that also releases carbon dioxide (CO_2), the largest component of greenhouse gas (GHG) emissions responsible for warming the Earth's surface and oceans and leading to climate change. Curtailing the use of fossil fuels may provide a double dividend: reduced CO_2 slowing the pace of global warming; as well as reduced AAPs preventing cardiovascular, respiratory and other disease (Bell et al., 2008; Haines et al., 2009). Commonly referred to as "co-benefits," these avoided costs to human health from AAP exposure can therefore also potentially play a role in underpinning policy decisions about GHG mitigation, including by providing specific dose- (or concentration)-response relationships needed to estimate likely population-wide benefits (Remais et al., 2014) as well as identify potentially vulnerable/susceptible populations. For example, based in part on such evidence anticipated AAP-related health co-benefits in Europe, the US, India and China have been shown to offset a large share of estimated GHG mitigation costs (Markandya et al., 2009; Jensen et al. 2013; Garcia-Menendez et al., 2015; Saari et al., 2015).

To our knowledge there is no recent review of the AAP SRMA literature examining its consistency with best-practice reporting and methods guidance. In order to contribute to further enhancing the utility of AAP SRMAs for the goal of health-protective policymaking, we reviewed the published SRMA literature addressing association of AAPs with adverse health outcomes in the general population, comparing methods and reporting used in practice with consensus SRMA recommendations and newly-emerging EH-specific guidance.

2. Methods

We searched Medline using PubMed with the pollutant search terms "ambient air pollution," "indoor air pollution," "particulate matter," "PM2.5," "black carbon," "PM10" "nitrogen dioxide," "NO2," sulfur dioxide," "SO2," "ozone," "O3," "carbon monoxide," and terms for systematic review and meta-analysis. We chose a start-date of 2009 to reflect the publication date of the PRISMA consensus reporting guidelines, a date also corresponding to a marked increase in publication of SRMAs in EH epidemiology (Sheehan and Lam, 2015). Our end-date was June 15, 2015. We did not restrict by language. We also hand-searched using reference lists.

We screened all resulting titles and abstracts and reviewed full texts of articles that met our pre-determined inclusion criteria: general, non-occupational populations, with exposure to one or more of the six commonly-measured AAP components – $PM_{2.5}$ (including black carbon), PM_{10}, CO, O_3, NO_2, SO_2 – addressing one or more health outcomes determined by study authors as adverse (including early markers of disease). To maintain the focus on AAP, we excluded SRMAs examining exposure to secondhand smoke, wildfire smoke, household or indoor sources of air pollution, PM chemical constituents, and acute poisonings. To preserve our focus on exposure-outcome association, we excluded reviews whose main outcome was effect modification or evaluation of the shape of distributions. Because our goal was to evaluate use of SRMA methods and reporting, we included only reviews for which SRMA was the main goal, and which used both SR and MA techniques; in other words, we excluded studies in which an SRMA was done as background to another study goal; and excluded SRs without MA (e.g., where available data were inadequate for a quantitative analysis), and MAs without SR (e.g., combining results across multi-center studies without an SR). We did not include studies for which only abstracts were available. Two authors (MS & JL) independently extracted data (differences were resolved by discussion and consensus), using purpose-designed data-extraction forms. Extracted data for each SRMA included: population characteristics, nature of AAP exposure, health outcomes, study designs used by underlying studies, and summary effect measures and confidence bounds, as well as responses to a questionnaire related to SRMA methods, reporting and strength of evidence evaluation.

The questionnaire included 22 items we consolidated from several sources of "good-practice" guidance for SRMAs, including the 27-item PRISMA checklist for SRMAs (Moher et al., 2009), the 35-point MOOSE consensus guidelines for SRMAs in observational epidemiology, the Blair et al. 1995 recommendations for EH SRMAs, as well as more recent emerging SRMA guidance for EH from the NTP (Rooney et al., 2014) and Navigation Guide (Woodruff and Sutton, 2014). In selecting the 22 items we aimed for a simple questionnaire that would incorporate the core recommendations in four domains: (i) SRMA article reporting, including implications of research; (ii) systematic review search, selection and extraction methods; (iii) meta-analytic statistical pooling methods and approaches to examining heterogeneity, study quality and risk of bias; and (iv) methods for evaluating the strength of evidence.

The 22 items, categorized into these four areas, include: (1) SRMA reporting (presence of six standard SRMA features including reported funding sources, table of underlying study characteristics; PRISMA study selection flow chart, forest plot of MA results by study, SRMA recommendations, and whether any SRMA guidelines were referenced); (2) systematic review literature search methods (four questions related to literature search, study selection and data extraction procedures);

(3) meta-analysis data pooling methods (seven questions referring to quality or risk-of-bias assessment, outcome ascertainment, exposure characterization, confounder adjustment and publication bias, and heterogeneity tests and models used); and (4) strength-of-evidence evaluation criteria (five questions addressing dose-response and magnitude, examination of negative- or no-effects, confidence in pooled effects, generalizability of findings, and study limitations). The specific guideline source for each of the 22 questions is provided in the table in Supplemental Material File 1.

Questions were designed to have up to four possible responses: "Yes" (Y), consistent with guideline; "Partial" (P), in some part consistent with guideline; "No″ (N), inconsistent with guideline; or cannot determine based on data provided (ND). For each question detailed definitions corresponding to published recommendations were developed in advance and provided to data extractors to facilitate consistency in extraction (Supplemental Material File 1). We tested questions and responses on a pilot group of several SRMAs to refine definitions, and then consistently evaluated all SRMAs accordingly. Responses were coded and combined in Microsoft Excel, and transferred to STATA version 10.0 (Statacorp, College Station, TX) for analysis.

We report results by question as number and share of SRMAs receiving each of the possible answers ("yes," "partial," "no" or "ND"). We also tracked all positive responses (i.e., "yes" plus "partial") compared to all responses. In addition, we evaluated evolution of responses over time by combining SRMAs into three groups roughly equal in size based on publication date (2009–2013; 2014; and 2015 through June 30), and reporting whether the trend was improvement (i.e., greater share of SRMAs reporting a positive response across the three periods: presented as an upward arrow), deterioration (i.e., lower share of SRMAs reporting a positive response: downward arrow), or no distinct trend detectable over the period (sideways arrow).

3. Results

Our search identified a total of 1136 articles, of which the full texts for 89 were reviewed and 43 met the inclusion criteria, including 6 identified through hand-searching (Fig. 1 and Table 1). Thirty-seven percent of included SRMAs were published between 2009 and 2013 (16 studies: Weinmayr et al., 2010; Ji et al., 2011; Mustafic et al., 2012; Vrijheid et al., 2011; Atkinson et al., 2012; Li et al., 2012; Pieters et al., 2012; Stieb et al., 2012; Takenoue et al., 2012; Hoek et al., 2013; Lai et al., 2013; Mehta et al., 2013; Park et al., 2013; Shah et al., 2013; Shang et al., 2013; and Zhu et al., 2013); 42% were published in 2014 (18 studies: Adar et al., 2014; Atkinson et al., 2014; Balti et al., 2014; Chen et al., 2014; Faustini et al., 2014; Favarato et al., 2014; Hamra et al., 2014; Hu et al., 2014; Janghorbani et al., 2014; Li et al., 2014; Liang et al., 2014; Park and Wang, 2014; Pedersen et al., 2014; Shin et al., 2014; Song et al., 2014; Wang et al., 2014; Yang et al., 2014; and Yu et al., 2014); and 21% were published from January 1 to June 30, 2015 (9 studies: Akintoye et al., 2015; Bowatte et al., 2015; Cui et al., 2015; Eze et al., 2015; Li et al., 2015; Lu et al., 2015; Mills et al., 2015; Provost et al., 2015; and Shah et al., 2015).

3.1. Health outcomes, AAP exposures and populations

Nearly half (49%) of selected reviews evaluated exposures to $PM_{2.5}$ and/or PM_{10} only, while 23% examined all six AAPs, 16% gases only (mainly NO_2) and 9% PM and gases (Fig. 2). Thirty-seven percent of SRMAs explored mortality and morbidity from cardiovascular (CVD) outcomes and related risk factors, including general CVD mortality, myocardial infarction, heart failure, stroke, heart rate variability, pregnancy-induced hypertension and pre-eclampsia, and carotid intima-media thickness (an early sign of atherosclerosis). A further

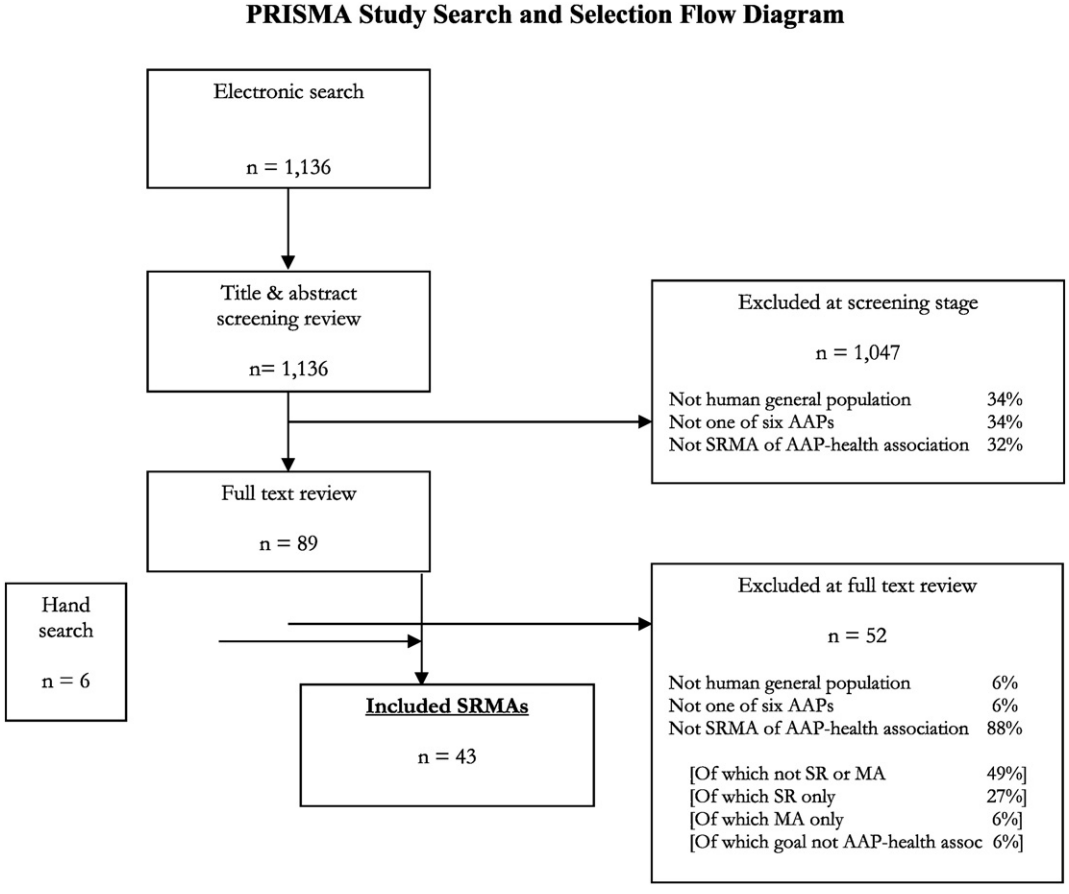

Fig. 1. AAP Epi SRMA Review: PRISMA Study Search and Selection Flow Diagram.

Table 1
Characteristics of included SRMAs.

SRMA first author	Pub year	AAP contaminant[a]	Health outcome	Population	Region	# studies in meta-analysis	Summary measure	Majority study type	Main reported pooled effect size (95%CI)[b]
Respiratory outcomes									
Weinmayr et al.	2010	PM_{10}	Asthma symptoms	Children	International	36	OR	CO	1.03 (1.01,1.05)
		NO_2				24			1.03 (1.00, 1.06)
Mehta et al.	2011	$PM_{2.5}$	ALRI	Children	International	4	RR	TS	1.12 (1.03, 1.30)
Ji et al.	2011	O_3	RESP hospitaliz.	Children and adults	International	6	% incr.	TS/CCr	2.03 (−0.21, 4.31)%
Takenoue et al.	2012	NO_2 (/10 ppb)	Asthma	Children	International	12	OR	CO	1.13 (1.03, 1.25)
Zhu et al.	2013	PM_{10}	COPD hospitaliz.	Adults	International	31	RR	TS	2.70 (1.90, 3.60)
			COPD mortality			31			1.10 (0.80, 1.40)
Song et al.	2014	PM_{10}	COPD hospitaliz.	Adults	International	44	OR	TS	1.02 (1.01, 1.02)
			COPD mortality			44			1.03 (1.02, 1.05)
Favarato et al.	2014	NO_2	Asthma prevalence	Children	International	18	OR	CO	1.04 (1.00, 1.11)
Bowatte et al.	2015	$PM_{2.5}$ (/2 μg/m3)	Asthma incidence	Children	International	5	OR	CO	1.09 (0.96, 1.23)
		NO_2				4			1.14 (1.00, 1.30)
		Black carbon				3			1.20 (1.05, 1.38)
Li et al.	2015	$PM_{2.5}$	COPD hospitaliz.	Adults	International	15	OR	TS	1.03 (1.02, 1.05)
			COPD mortality			7	% incr.		2.5% (1.5%, 3.5%)
Cardiovascular outcomes									
Mustafic et al.	2012	CO	Myocardial infarction	Adults	International	20	RR	TS/CCr	1.05 (1.03, 1.07)
		NO_2				21			1.01 (1.01, 1.02)
		SO_2				14			1.01 (1.0, 1.02)
		PM_{10}				17			1.01 (1.0, 1.01)
		$PM_{2.5}$				13			1.02 (1.02, 1.04)
		O_3				19			1.00 (1.00, 1.01)
Pieters et al.	2012	$PM_{2.5}$	Heart rate variability	Adults	International	13	% decr.	CO	−2.44 (−3.76, −1.12)
						13			
Li et al.	2012	PM_{10}	Stroke	Adults	International	15	OR	TS/CCr	1.0 (1.00,1.00)
		$PM_{2.5}$				15			1.01(1.00,1.01)
Shah et al.	2013	CO	Heart failure	Adults	International	18	RR	TS/CCr	1.02 (1.01, 1.03)
		SO_2 (/10 ppb)				14			1.01 (1.00, 1.03)
		NO_2 (/10 ppb)				18			1.01 (1.00, 1.01)
		$PM_{2.5}$				10			1.02 (1.01, 1.02)
		PM_{10}				22			1.01 (1.00, 1.02)
		O_3 (/10 ppb)				18			1.00 (1.00, 1.1)
Hoek et al.	2013	$PM_{2.5}$	CVD mortality	Adults	International	10	RR	CO	1.15 (1.04, 1.27)

SRMA first author	Pub year	AAP contaminant[a]	Health outcome	Population	Region	Study design, number in meta-analysis	Summary measure	Majority study type	Main reported pooled effect size (95%CI)[b]
Yang et al.	2014	CO	Stroke hospitalization or mortality	Adults	International	34	RR	TS	2.96 (0.70, 5.27)
		SO_2 (/10 ppb)							1.53 (0.66, 2.41)
		NO_2 (/10 ppb)							2.24 (1.16, 3.33)
		$PM_{2.5}$							1.20 (0.22, 2.18)
		PM_{10}							0.58 (0.31, 0.86)
		O_3							2.45 (0.35, 4.6)*
									I only
Pedersen et al.	2014	$PM_{2.5}$	Pregnancy-induced hypertension	Women	International	10	RR	CO	1.31 (1.14, 1.50)
Shin et al.	2014	$PM_{2.5}$	Non-fatal stroke	Adults	International	20	RR	NS	1.06 (1.00, 1.13)
Wang et al.	2014	$PM_{2.5}$	Stroke hospitaliz	Adults	International	45	RR	TS/CCr	1.00 (1.00, 1.01)
			Stroke mortality						1.01 (1.01, 1.02)
		PM_{10}	Stroke hospitaliz						1.01 (1.00, 1.01)
			Stroke mortality						1.00 (1.00, 1.01)
Liang et al.	2014	$PM_{2.5}$	SBP	Adults	International	22	SBP increase	P	1.39 (0.87, 1.91)
			DBP			22	DBP increase		0.90 (0.49, 1.30)
Yu et al.	2014	$PM_{2.5}$ (/10 mg/m3)	Ischemic stroke	Adults	International	19	OR	TS/CCr	1.02 (1.00, 1.05)
		PM_{10} (/10 mg/m3)							1.01 (1.00, 1.03)
Shah et al.	2015	CO	Stroke:	Adults	International	94	RR	TS	1.02 (1.00, 1.03)
		SO_2 (/10 ppb)	hospital admission						1.02 (1.01, 1.03)
		NO_2 (/10 ppb)	and mortality						1.01 (1.01, 1.02)
		$PM_{2.5}$							1.01 (1.01, 1.01)
		PM_{10}							1.00 (1.00, 1.00)
		O_3 (/10 ppb)							1.00 (1.00, 1.00)
Provost et al.	2015	$PM_{2.5}$ (/5 μg/m3)	Carotid intima-media thickness	Adults	International	12	% incr.	CS	1.66 (0.86, 2.46)%
Akintoye et al.	2015	$PM_{2.5}$	Carotid intima-media thickness	Adults	International	12	Increase	CS/CO	22.52 (−1.26, 46.29)um
Other or mixed outcomes									
Vrijheid et al.	2011	NO_2	Congenital anomalies	Fetus/infants	International	4	OR	CC	1.20 (1.02, 1.42)
		PM_{10}				4			1.14 (1.01, 1.28)
Stieb et al.	2012	PM_{10} (/20 μg/m3)	LBW	Fetus/infants	International	9	OR	CO	1.10 (1.05, 1.15)

Table 1 (*continued*)

SRMA first author	Pub year	AAP contaminant[a]	Health outcome	Population	Region	Study design, number in meta-analysis	Summary measure	Majority study type	Main reported pooled effect size (95%CI)[b]
Atkinson et al.	2012	PM_{10}		Adults and	China	82	% incr.	TS	
		$PM_{2.5}$	Mortality	children					PM_{10}:
		SO_2	Hospital admissions						0.27 (0.12, 0.42)% [All mortality]
		NO_2	Community care						0.86 (0.34, 1.39)% [RESP mortality]
		O_3	Asthma hospitaliz.						0.36 (0.09, 0.62)% [CVD mortality]
		CO							
Lai et al.	2013			Adults and	China		RR	CO	All-cause mortality:
		PM_{10}	Mortality	children		22			1.00 (1.00, 1.00) [PM_{10}]
		NO_2	Hospital admissions			23			1.01 (1.01, 1.02) [NO_2]
		SO_2	ER admissions and visits			9			1.01 (1.00, 1.01) [SO_2]
		O_3	Adverse birth outcomes			10			1.00 (1.00, 1.01) [O_3]
Shang et al.	2013	$PM_{2.5}$	All cause mortality	Adults	China	9	RR	TS/CCr	0.38 (0.31, 0.45)
			CVD mortality			7			0.44 (0.33, 0.54)
			RESP mortality			7			0.51(0.30, 0.73)
Park et al.	2013	PM_{10}	Mortality	Adults	Asia	12	RR	TS/CCr	1.01 (1.00, 1.01)
Faustini et al.	2014	NO_2	All-cause mortality	Adults	International	19	RR	CO	1.04 (1.02, 1.06)
			CVD mortality						1.13 (1.09, 1.18)
			RESP mortality						1.03 (1.02, 1.03)
Atkinson et al.	2014	$PM_{2.5}$	All-cause mortality (23 outcomes)	Adults	International	110	RR	TS	1.04 (0.52, 1.56)
			CVD mortality						0.84 (0.41, 1.28)
			RESP mortality						1.51 (1.01, 2.01)
Li et al.	2014	NO_2	Diabetes mortality	Adults	International	5	RR	TS/CCr	1.04 (1.01, 1.06)
		SO_2				3			1.03 (1.00, 1.06)
		O_3				3			1.07 (1.02, 1.11)
		CO				3			1.04 (1.00, 1.09)
		$PM_{2.5}$				4			1.08 (1.03, 1.13)
		PM_{10}				4			1.01 (1.00, 1.02)
Hu et al.	2014	O_3	Hyper. Pregnancy	Pregnant	International	7	OR	CO	1.09 (1.05, 1.13)
		CO		women		4			1.79 (1.31, 2.45)
		NO_2 (/10 ppb)				5			1.16 (1.03, 1.30)
		SO_2 (/2.25 ppb)				1			1.13 (1.01, 1.25)
		PM_{10}				6			1.10 (0.96, 1.26)
		$PM_{2.5}$				5			1.15 (0.94, 1.40)
Janghorbani et al.	2014	NO_2	Diabetes T2	Adults	International	17	RR	CCr/CO	1.05 (1.02, 1.08)
		$PM_{2.5}$							1.05 (0.99, 1.01)
		PM_{10}							1.01 (1.00, 1.01)
		O_3							1.07 (1.05, 1.09)
Hamra et al.	2014	$PM_{2.5}$	Lung cancer mortality	Adults	International	9	RR	CO	1.08 (1.00, 1.17)
		PM_{10}				13			1.09 (1.04, 1.14)
Adar et al.	2014	$PM_{10\text{-}2.5}$	Mortality	Adults	International	19	RR	TS/CCr	1.01 (1.00, 1.01)
Chen et al.	2014	SO_2 (/1 μg/m3)	Congenital anomalies	Pregnant	International	4	OR	CCr	NO_2-coarctation of aorta
		PM10		women					
		CO							1.20 (1.02, 1.41)
		O_3 (/5 ppb)							
		NO_2 (/10 ppb)							
Balti et al.	2014	$PM_{2.5}$	Diabetes T2	Adults	International	5	RR	CS/CO	1.11 (1.03, 1.20)
		NO_2				5			1.13 (1.04, 1.22)
Park et al.	2014	$PM_{2.5}$	Diabetes T2	Adults					
		NO_2							
Lu et al.	2015	$PM_{2.5}$	Total mortality	Adults	China	59	RR	TS	0.40 (0.22, 0.59)
									0.63 (0.33, 0.91)
									0.75 (0.39, 1.11
		PM_{10}	CVD mortality						
			RESP mortality						0.36 (0.26, 0.46)
									0.36 (0.24, 0.49)
									0.42 (0.28, 0.55)
Mills et al.	2015	NO_2	Total mortality	Adults	International	31	% incr.	TS	0.71 (0.43, 1.00)%
			CVD mortality			28			0.88 (0.63, 1.13)%
			RESP mortality			26			1.09 (0.75, 1.42)%
Eze et al.	2015	$PM_{2.5}$	Diabetes T2	Adults	Europe, North	3	RR	CS/CC	1.10 (1.02, 1.18)
		NO2			America	4			1.08 (1.00, 1.17)
Cui et al.	2015	$PM_{2.5}$	Lung cancer mortality	Adults	International	12	RR	CO	1.09 (1.06, 1.11)
		PM_{10}				7			1.05 (1.03, 1.07)

Abbreviations: Contaminants - CO: Carbon monoxide; NO_2: Nitrogen dioxide; O_3: Ozone; $PM_{2.5}$: Particulate matter <2.5 μm; PM_{10}: Particulate matter <10 μm.
Outcomes - CANC: Cancer; CVD: Cardiovascular disease; RESP: Respiratory; LBW: Low birth weight; ALRI: Acute Lower Respiratory Infection; SBP: systolic blood pressure; DBP: diastolic blood pressure; ER: Emergency room.
Study type - CC: Case control; CCr: Case-crossover; CO: Cohort; CS: Cross-sectional; NS: Not stated; TS: Time-series; P: Panel.
Effect estimates - OR: Odds ratio; RR: relative risk; % incr.: percent increase; % decr: percent decrease.

[a] Unless otherwise noted, AAP contaminant units are as follows: CO: per $\mu g/m^3$; NO_2, SO_2, O_3, $PM_{2.5}$ and PM_{10}: per 10 $\mu g/m^3$.

[b] Pooled effect sizes shown are the principal chemical exposure and/or health effect associations reported in reviews.

30% examined mortality and morbidity from respiratory outcomes, including general respiratory mortality, asthma symptoms, chronic obstructive pulmonary disease (COPD), and reduced peak expiratory flow. All-cause mortality was examined in 14%, type-2 diabetes in 12%, and congenital anomalies in 5% of reviews. Most (73%) SRMAs evaluated exposures and outcomes in adults, while infants or children alone or in combination with women were the focus of 27% of SRMAs. Few reviews limited geographic coverage; however, most underlying study populations were from North America, Europe and/or Asia, although three SRMAs covered China only and one Asia only. Over half of reviews examined all or predominantly time-series and case-crossover studies, while the remainder examined a mix of cohort, case-control and cross sectional studies. Most selected reviews reported pooled estimated relative risks (RRs, 62%), or pooled odds ratios (ORs, 27%).

The mean number of "yes" answers to the 22-point questionnaire for the group of 43 SRMAs was 12.6 (range 5–19), or 57% of questions (Table 2). When considering all positive responses ("yes" and "partial") this increased to 16.3 (range 10–21), or 74% of questions. As shown in Table 2, the mean number of "yes" answers increased from 11.7 (average for 2010–2013) to 12.8 (first half of 2015), with the "no" and "ND" combined response decreasing from 7.0 to 4.7 over the same period. In the case of eight questions (36%) there was a trend toward an increased share of "yes" responses over the period, and for only three questions (18%) was the trend declining. Four SRMAs received 17 or more "yes" answers (a rating equivalent to >75% of total questions), and this increased to 25 SRMAs, or 58% of those included in this review, when combining "yes" and "partial" answers. A majority of the latter were published in the last 2 years.

3.2. Systematic review and meta-analysis reporting

Most SRMAs (91%) provided a summary table with main characteristics of the underlying studies, and nearly all (95%) provided forest plots for the meta-analysis; these shares were relatively constant over the period (Table 2). A majority (72%) also reported sources of financial support for the study (in all cases government or academic institutions), and the share increased with time. A PRISMA study selection flow diagram was provided in 58% of studies, and the share increased over time. Twenty-eight percent of studies provided recommendations that went beyond suggesting the need for further research (made by nearly all studies) to include practice, policy or specific suggestions for improved underlying study design or reporting. Thirty-five percent of SRMAs ($n = 15$) made reference to an SRMA guideline, most often the PRISMA statement (although several referenced the MOOSE guidelines, or to both); this share did not change over time.

3.3. Systematic review search, selection and extraction methods

Thorough and transparent study search methods, clearly-described study selection criteria and procedures, and use of two or more authors to undertake study review and data extraction were reported in over half of SRMAs included in our review (51%, 63%, and 53% respectively), and the trend for all three questions was an increased share of "yes" answers over time (Table 2). The share for both search and selection procedures rose to 86% and 88% of SRMAs, respectively, when considering both "yes" and "partial" responses. Only 7% of SRMAs (33% when considering both "yes" and "partial" answers) reported use of piloted purpose-designed extraction forms, with little observed change over time.

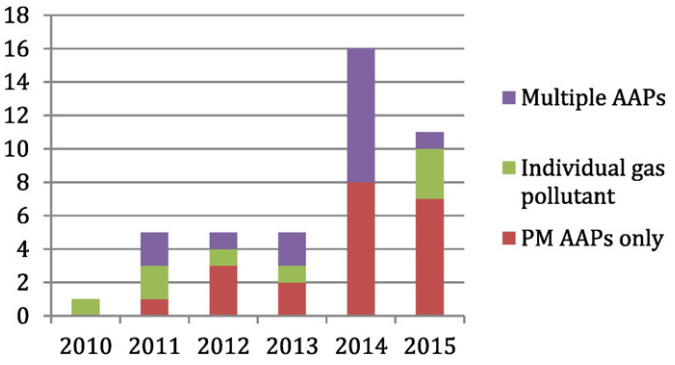

Fig. 2. AAP SRMAs by publication year (2010 through mid 2015, $n = 43$).

3.4. Meta-analysis data pooling methods

A large majority of SRMAs (97%) reported use of statistical tests to evaluate cross-study heterogeneity and appropriate use of random effects models to pool data when substantial heterogeneity was observed (Table 2). Most also pursued understanding the sources of heterogeneity through stratification and/or meta-regression (72%, increasing to 95% when considering all positive responses). Just 28% of SRMAs ($n = 12$) reported carrying out a quality or risk-of-bias assessment, although the share increased over time (to 44% of SRMAs published in the first half of 2015). Among all 43 SRMAs, potential confounders affecting underlying studies were examined and reported by 53% (88% when considering all positive responses), health outcome ascertainment was assessed by 58% (all positive responses 84%) and exposure metrics used in underlying studies were evaluated in 53% (all positive responses 76%) of SRMAs. There was a decline in the share of "yes" responses over time for confounding evaluation, no change for outcome ascertainment, and wide variability with no detectable trend for exposure metrics. Examination and reporting of publication bias was undertaken in 80% of SRMAs (with the majority of studies reporting use of funnel plots), with little change observed over time.

3.5. Strength-of-evidence evaluation

Dose-response relationships and magnitude of effects across studies were examined in 40% of SRMAs, although this reached 82% considering all positive responses (Table 2). No- or negative-effects were discussed in 37% of SRMAs. For both, the share of "yes" responses increased notably over the time period. Confidence in observed effects was discussed in 63% (reaching 95% considering all positive responses) though this share declined with time. The generalizability of SRMA findings was addressed by 63% of SRMAs and the share increased with time. Most SRMAs (95%) addressed limitations; however, only 58% included a thorough discussion and the share of positive responses declined over the period.

4. Discussion

In this systematic review of AAP SRMAs published from 2009 through mid-2015 we identified a total of 43 studies using both SR and MA techniques examining associations of exposure to the main six measured AAPs and adverse health outcomes in general human populations. Over 60% of identified SRMAs were published in the 1.5 years between the outset of 2014 and our search end-date of June 30, 2015, indicating rapidly growing use of these methods in AAP epidemiology. For the group of 43 SRMAs, the average number of positive ("yes" plus "partial") answers was 16.3 of 22 questions (74%, range 10–21) and we observed an increasing trend in positive responses over the study period. However, while our overall assessment of AAP SRMA methods and reporting is positive and suggestive of a growing degree of concordance with best practice, we noted several areas for improvement.

Regarding reporting, a PRISMA study-selection flow chart was provided by <60% of SRMAs, though the trend was increasing. Lack of detailed information on study selection jeopardizes transparency and replicability. Journal space limitations may be one factor in this finding; however, any such constraint should be manageable through provision

Table 2
Evaluation of AAP SRMA reporting, methods, and strength of evidence: 22-item questionnaire (2009 through mid-2015).

Recommendation category/item	Number of SRMAs with response: (share of total 43 SRMAs)			Trend 2009-mid-2015
	"Yes"	"Partial"	"No" or "ND"	
1. *SRMA reporting*				
Reported funding sources (Q 1)	31 (72%)	4 (9%)	8 (19%)	↑
Referred to SRMA guideline (Q 2)	15 (35%)	0 (0%)	28 (65%)	↔
Included SR PRISMA diagram (Q 3)	25 (58%)	0 (0%)	18 (42%)	↑
Included study summary table (Q 4)	39 (91%)	0 (0%)	4 (9%)	↔
Included MA forest plot (Q 5)	41 (95%)	0 (0%)	2 (5%)	↔
Provided recommendations (Q 6)	12 (28%)	22 (51%)	9 (21%)	↑
2. *SR methods*				
Conducted thorough search (Q 7)	22 (51%)	15 (35%)	6 (14%)	↑
Carried out robust selection (Q 8)	27 (63%)	11 (26%)	5 (12%)	↑
Reported 2 reviewers (Q 9)	23 (53%)	2 (5%)	18 (42%)	↑
Piloted extraction forms (Q 10)	3 (7%)	11 (26%)	29 (67%)	↔
3. *MA methods*				
Addressed confounding (Q 11)	23 (53%)	15 (35%)	5 (12%)	↓
Addressed outcome ascertainment (Q 12)	25 (58%)	11 (26%)	7 (16%)	↔
Addressed exposure metrics (Q 13)	23 (53%)	10 (23%)	10 (23%)	↔
Carried out quality/risk of bias (Q14)	12 (28%)	0 (5%)	31 (72%)	↑
Reported publication bias (Q15)	35 (80%)	1 (2%)	7 (16%)	↔
Tested for heterogeneity (Q 16)	42 (97%)	0 (0%)	1 (3%)	↔
Pursued heterogeneity sources (Q 17)	31 (72%)	10 (23%)	2 (5%)	↔
4. *Strength-of-evidence*				
Evaluated dose-response (Q 18)	17 (40%)	18 (42%)	8 (18%)	↑
Evaluated negative or no-effects (Q 19)	16 (37%)	0 (0%)	27 (63%)	↑
Discussed limitations (Q20)	25 (58%)	16 (37%)	2 (5%)	↓
Discussed generalizability (Q 21)	27 (63%)	0 (0%)	16 (37%)	↑
Discussed confidence in effects (Q 22)	27 (63%)	14 (33%)	2 (5%)	↓
Average for 22 questions				
2010–2013	11.7 (53%)	3.3 (15%)	7.0 (32%)	
2014	13.3 (60%)	3.7 (17%)	5.0 (23%)	
2015 (Jan–June only)	12.8 (58%)	4.6 (21%)	4.7 (21%)	
Combined average	12.6 (57%)	3.7 (17%)	5.7 (26%)	

of supplemental material online, a common practice for many journals. In addition, while most SRMAs provided concrete recommendations, these largely focused on future research. Less than one-third went beyond research recommendations to address policy, practice and improved study design. While specific SRMA goals and findings varied, nevertheless, this represents a missed opportunity. Because of their synthetic perspective, SRMAs are ideally designed to indicate to underlying study authors specific improvements in future study design or reporting (e.g., more consistent exposure metrics, outcome ascertainment and dose-response assessment, as recommended by Eze et al. 2015; need for additional studies in low- and middle-income countries, as provided by Shah et al., 2015), as well as suggesting directions or implications for policy and practice (e.g., applicability of an identified concentration-response function for burden of disease estimates, as provided by Favarato et al., 2014).

In the case of SR methods, we found only slightly over half of SRMAs reported who extracted underlying study data; nearly all of these reported two-person independent review and extraction. A very small share (7%) reported using piloted, purpose-designed SRMA extraction forms (although in total one-third of SRMAs reported using extraction forms). Together, these results suggest some possibility for error in data extraction. While costly in terms of resources, use of duplicate independent extraction has been considered the gold standard for SRMAs. However more recently, the NTP suggests data be extracted by one reviewer with a quality assurance procedure as part of an SRMA protocol (Rooney et al., 2014). One study in our review reported using a similar approach, with extraction of risk estimates by one author along with a well-defined review and accuracy-checking process (Hamra et al., 2014). Further research regarding validity of SR procedures designed to minimize study data-extraction error would be useful. Regardless of approach used, SRMA authors should be encouraged to fully report methods for data extraction.

A surprisingly low share of SRMAs (28%) reported undertaking a separate quality or risk-of-bias assessment. Such an assessment, examining key sources of bias, misclassification and other potential error, is a core recommendation of PRISMA and MOOSE SRMA guidance (Moher et al., 2009; Stroup et al., 2000) as well as of emerging NTP and Navigation Guide recommendations (Rooney et al., 2014; Woodruff and Sutton, 2014). Of the 12 SRMAs reporting quality assessments, four cited use or modification of the Newcastle-Ottawa Scales (Wells et al., undated) one of which also cited the Cochrane Collaboration risk-of-bias tool (Higgins et al., 2011). The remaining eight described a quality or risk-of-bias review process that evaluated several study design parameters without citing a specific tool. Among those that did not carry out a formal quality review, a majority examined the four individual elements of such a review included in our questionnaire (exposure characterization, health outcome ascertainment, examination of confounders and publication bias). However, we found that of the 12 SRMAs that undertook formal quality reviews, 75% evaluated these parameters to some degree (either "yes" or "partial" responses to all four items) while of the 31 SRMAs that did not undertake a separate quality review only 52% did a similarly comprehensive review of these four parameters. This suggests a formal quality review may be more likely to lead to thorough treatment of quality and risk-of-bias parameters. Several SRMAs authors noted the lack of specific validated risk-of-bias tools for AAP or EH SRMAs which likely contributed to the low share of SRMAs reporting a separate quality review or risk-of-bias analysis.

In recent years, substantial work has been undertaken to develop risk-of-bias recommendations tailored specifically for EH studies as well as empirically demonstrating their application through case studies (Rooney et al. 2014; Woodruff and Sutton, 2011; Johnson et al. 2014; Koustas et al. 2014). Ideally, EH SRMA, including those addressing AAP, will begin to draw from this work to develop, validate and incorporate risk-of-bias assessment as part of their evaluation process. In our

review we found some SRMAs reported undertaking quality assessments but did not report any particular findings or provide evidence that the quality issues were reflected in evaluation of cross-study heterogeneity.

Regarding MA methods, we found that evaluating heterogeneity with a statistical test, and using random effects models when substantial heterogeneity was found, seems to be standard practice in the published peer-reviewed AAP SRMA literature. This compares favorably with a review of the occupational health literature a decade ago that found many reviews used fixed effects models even in the presence of substantial statistically-confirmed heterogeneity (McElvenny et al., 2004). However, a somewhat lower share of the AAP SRMAs we evaluated performed extensive evaluation of sources of heterogeneity. Ideally, this would be done based on issues identified in a quality/risk-of-bias review.

Most SRMAs did not fully evaluate (i.e., "yes" response) the strength-of-evidence criteria we included in our questionnaire, including generalizability, dose-response relationships, addressing no- or negative effects, and assessing confidence in findings. However, the majority of reviews addressed these questions at least partially, and there was evidence of increased attention (greater number of "yes" responses) to several of these recommendations over time. In the context of SRMA utility for policy, of particular relevance is dose-response assessment; a number of SRMA authors observed that linear dose-response relationships were often simply assumed in underlying studies rather than being examined. Generalizability of findings is also important in policy contexts; SRMA authors commonly noted the underlying literature lacked comprehensiveness in geographic terms, with studies in many low- and middle-income countries lacking. We did not include in this study meta-analyses of multi-center studies, which may be more appropriate for use populations that share their specific characteristics. Incorporating the above concepts as recommended aspects of SRMAs has emerged more recently from the work of the NTP and Navigation Guide; case studies prepared by these groups have been the first SRMAs to systematically incorporate these criteria (Johnson et al. 2014; Koustas et al. 2014; Lam et al. 2014; Vesterinen et al. 2015), all of which have direct relevance for translating pooled effect estimates into practical policy implications. As additional case studies are published demonstrating how these are to be evaluated, including in the AAP field, it is expected that more studies will incorporate them into their evaluation.

Several other recent reviews of reporting and methods have been carried out in EH and other fields. Our review of 48 EH SRMAs found a majority of studies followed most general SRMA guidance of the PRISMA and MOOSE consensus statements, although we identified weaknesses in problem formulation, study search, selection and data extraction, dealing appropriately with differences in exposure metrics, and other risks of bias as well as integrating policy implications (Sheehan and Lam, 2015). A similar review of SRMAs in the occupational health field that identified 60 OH SRMAs found limitations and inconsistencies in exposure characterization and inadequate and unclear adjustment for confounders (McElvenny et al., 2004). A review of SRMA in psychiatric epidemiology found substantial heterogeneity among studies, and noted particularly wide variety and poor comparability of outcome measurement instruments (Brugha et al., 2012). Finally, a recent review of risk-of-bias assessments in epidemiological studies found assessment conclusions were often poorly integrated into study findings (Katikireddi et al., 2015). Our results broadly echo these findings, although we identified a number of strengths, and a notable improving trend across multiple reporting and methods parameters.

Regarding AAP SRMA findings, reported pooled associations were generally positive and statistically significant, although of relatively small magnitude per increment of measured AAP pollutant. In the context of very high pollution levels in some world regions, as well as widespread prevalence of many of the health outcomes addressed, small effect sizes represent a substantial disease burden. This review also provides an indication of focus in the synthesized evidence. In particular, while past reviews have focused on all-cause, CVD, and respiratory mortality associated with PM, morbidity due to a number of diseases widespread in populations have now been evaluated in the AAP SRMA literature (e.g., non-fatal stroke, type-2 diabetes, hypertension in pregnancy, childhood asthma symptoms, risk of atherosclerosis). Many AAP SRMAs noted underlying studies were largely undertaken in the large cities of high-income countries, while the highest levels of air pollution worldwide are found in low- and middle-income countries, including China, India, Pakistan, Iran and other countries, in both large mega-cities but also in industrial regions (WHO, 2015b). Our review suggests a rapidly growing literature in Asia and in particular China, however, well-designed epidemiological studies and SRMAs are required to better understand the specific health risks associated with AAP in other low- and middle-income countries.

This review of SRMA methods is subject to several limitations. Given the rapidly-developing AAP epidemiology literature and the recent significant increase in use of SRMAs (we identified 18 published in 2014 alone), we may not have identified all SRMAs actually published over our selected time period. In addition, another slightly different set of reporting and methods questions might have resulted in a somewhat different result. However, we chose major items that in most cases were common to multiple guidelines, minimizing this risk. Our questionnaire aimed to balance specificity and practicality of implementation, and several parameters combined multiple concepts (e.g., a "yes" response for study search methods was wide in terms of databases used (three or more) and time periods (10 years or more), as well as unrestricted by language). In addition, subjectivity of reviewer judgment cannot be completely eliminated (although our overall initial disagreement was <5% of responses). Given these factors, we cannot ensure that all studies with parameters rated "yes" are entirely the same qualitatively. For this reason, we also tracked all positive responses ("yes" plus "partial") and have reported this result as our principle finding. We found the structure of the questionnaire and its detailed response descriptions (Supplemental Material File 1) provided a sound framework for reaching consensus. In addition, based on the findings of our earlier study, we had incorporated components of the NTP and Navigation Guide SRMA guidance into our questionnaire. While application of both methods are in early stages, experience gained from applying these methodologies to-proof-of concept case studies (Lam et al., 2014; Vesterinen et al. 2015) helped with interpretation of tools and development of our response definitions. Additional case studies and testing of these tools, including for AAP, will help to more fully and reliably capture these elements. Finally, we were not able to distinguish for a number of questions whether SRMA authors did not carry out the item as recommended, or did so but did not report this (e.g., number of data extractors, use of SRMA guidelines), which reinforces the need for comprehensive reporting of methods in SRMA.

5. Conclusions

On the whole, SRMA reporting methods used in the published AAP SRMA literature demonstrate strong concordance with PRISMA and MOOSE consensus statement methods and more recent reporting recommendations, and we found suggestive evidence that this has improved with time as guidance is taken up by researchers. Low uptake of the recommendation for a separate quality/risk of bias assessment of underlying studies was observed, however, as well as suggestive evidence that SRMAs without such an assessment may be less thorough in their review of these parameters. However, an improving trend was evident in this recommendation, as well as strength-of-evidence parameters from more recently-introduced recommendations. Development, validation and dissemination of an EH (AAP) specific risk-of-bias tool would be a useful contribution and could enhance the utility of AAP SRMAs for the purpose of environmental health policy making.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.envint.2016.02.016.

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