

Review article

Awareness of and potential for dependent error in the observational epidemiologic literature: A review

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ABSTRACT

Purpose: Measurement error discussions often assume classification errors of key variables are independent. Yet, small amounts of dependent error can create large biases in effect estimates. The purpose of this review was to evaluate frequency of measurement error discussions and potential for dependent error in the observational literature.

Methods: Two samples of articles analyzing exposure-outcome contrasts were collected: a random sample ($n = 100$) from high-impact epidemiology and medical journals (June 2015–July 2016), and a citation-based sample ($n = 39$) of studies citing one of two prominent dependent misclassification articles (through July 2016). We extracted study details, recorded measurement error mentions, and qualitatively assessed dependent error potential.

Results: Measurement error was often discussed. No random sample articles explicitly mentioned dependent error, compared with 59% of the citation-based sample. The random sample was found to be at low risk of exposure-outcome (15% plausible/probable) but increased risk for exposure-confounder (38% plausible/probable) dependency. The citation-based sample was at higher risk for dependent error (exposure-outcome: 46% plausible/probable; exposure-confounder: 61% plausible/probable).

Conclusions: Although measurement error was frequently mentioned, potential impact on observed results was rarely discussed in-depth or quantified. Dependent error mentions were rare, even among studies deemed susceptible. Further education and steps to avoid dependent error are needed.

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Background

The goal of most etiologic, observational research is to estimate a valid and precise measure of the effect of an exposure on an outcome. While error reduction efforts occur during study design, data collection, and statistical analysis, both random and systematic error occur at some level in all studies. One common source is measurement error. While most studies have some measurement error, impacts on observed estimates vary based on the extent and mechanism of the error [1–5]. Dependent error (when error in one variable is correlated with error in a second) in particular warrants attention due to potential for strong biases in effect estimates (see [Supplement for additional dependent error background](#)).

In spite of the threat to validity, measurement error and potential impact on results may often be unacknowledged in published findings [6–8] and how often potential for dependency in measurement errors is explored in observational research is largely unknown. The purpose of this review was to (a) evaluate the frequency of measurement error mentions in published etiologic observational studies, (b) understand the nature of these mentions, (c) determine whether any evaluations note potential for dependent error/misclassification, and (d) assess the potential for dependencies in classification of key variables based on available information in a select group of journals from the epidemiologic and medical literature.

Methods

Study selection: high-impact journal random sample

We conducted an electronic database search of PubMed to identify publications from seven high-impact journals published between June 2015 and July 2016. An initial review of article titles

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and abstracts was conducted. Records that were not primary research articles were excluded. A random sample of 100 articles was drawn from the remaining 2124 results after screening with no stratification by journal or overall journal type. Each article's full text was reviewed. An article was removed from the sample if, on review, it was not a primary research article or it met one of the full exclusion criteria ([Supplement, Methods](#)). Removed articles were replaced via random sampling of the remaining screened articles to yield a final 100 articles meeting inclusion criteria ([Supplement Figure 1](#)).

Study selection: citation-based sample

We used Google scholar to identify studies published between January 1992 and July 2016 citing one of two prominent research articles by Kristensen [9] and Brenner [10] on dependent misclassification. After initial review to include only English language, peer-reviewed publications, full-text review using the same inclusion and exclusion criteria as the random sample, yielded a final sample of 39 articles ([Supplement, Methods & Figure 1](#)).

Data collection

A single abstractor reviewed articles and entered study details into an electronic database (full abstraction details in [Supplement and Methods](#)). In addition, the abstractor recorded details on the manuscript's evaluation of measurement error, including (1) whether measurement error/misclassification was evaluated/discussed, (2) error mechanisms (if any) mentioned (nondifferential, differential, independent, and/or dependent), (3) pertaining to which variables (exposure, outcome, and/or confounder(s)), (4) location of assessment (introduction, methods, results, discussion, and/or supplement), and (5) nature of the evaluation (discussion-based, sensitivity analysis, regression calibration, or quantitative bias analysis). For citation-based articles, the usage of the citation within the article was also recorded.

Dependent error assessment

After article data were abstracted, the abstractor made a qualitative assessment regarding the likelihood of exposure-outcome dependent error and exposure-confounder dependent error (unlikely, plausible, or probable). Assessment was informed by method and timing of data collection for key variables, particularly if collected via the same instrument at the same time point. In addition, the assessment was informed by plausibility of a shared error mechanism between variables (i.e., yea-/nay-saying, social desirability, common rater, same instrument, shared biologic sample, etc.) [11].

Quality control

The review protocol was written before the study and followed, whenever possible, preferred reporting items for systematic reviews and meta-analysis (PRISMA). A selection of articles (10%) was reviewed by another abstractor blinded to the original abstractor's responses. Abstractor agreement was high (>80%). List of reviewed articles and the full abstraction database are available on request.

Results

Random sample (high-impact journals)

Of the 100 randomly sampled articles, 59 were from epidemiology-focused and 41 from medical-focused journals.

Sampled articles reflected a wide range of topics, including social/behavioral (30%), health services/policy (21%), cardiology (16%), environmental/occupational (15%), and perinatal/pediatric (15%). Over three-quarters mentioned potential for misclassification or measurement error for at least one variable ([Table 1](#)). Of these, 69% noted potential for independent nondifferential misclassification, 38% specified independent differential misclassification, and 29% mentioned measurement error broadly. While overall measurement error mentions were more common among epidemiology-focused journals, medical-focused journals more frequently specified an error mechanism.

The review revealed no definite, direct mention of dependent error concerns. One instance was determined a probable mention. In addition, independence of error mechanisms was often unstated, but likely assumed. Only one article explicitly clarified an error mechanism was "independent."

When exploring which variables were highlighted as having measurement error concerns, both exposure (78%) and outcome error (70%) assessments were common ([Table 1](#)). Confounder error concerns were rare (9%). This trend was similar by journal type.

Measurement error mentions occurred most commonly in discussion sections and often focused on validity or accuracy of measurement methods as a study strength or limitation. Evaluation of measurement error impact was often qualitative (77%). Roughly a quarter of articles conducted sensitivity analyses which most often entailed restricting data based on information quality or altering variable definitions to see whether initial results changed. No studies used quantitative bias analyses. Trends were consistent by journal type.

When we evaluated articles for dependent error potential, exposure-outcome dependent error was unlikely in most of studies (85%) with little variation by journal type ([Table 2](#)). Using different methods to measure exposure and outcome often reduced dependent error risk (e.g., self-reported exposure and outcome via medical instrument). For prospective studies, separation between exposure and outcome data collection time points further reduced concerns.

Exposure-confounder dependent error likelihood was more common than exposure-outcome (23% plausible and 15% probable risk for exposure-confounder dependence; [Table 2](#)). Increased risk was often due to collecting exposure and confounder at the same time using the same instrument. Examples included self-reported dietary habits with one nutrient as an exposure and other dietary factors as confounders, variables documented within medical records from the same clinical encounter, and one biological sample providing both exposure and confounder data (i.e., blood). In some studies, focus on confounders expected to have minimal error (i.e., age) reduced concerns. Exposure-confounder dependent error risk was slightly increased among epidemiology compared with medical-focused journals.

Citation-based sample

Articles citing Brenner or Kristensen reflected a wide range of topics, although many were social/behavioral (41%) or environmental/occupational (38%). As expected, 100% mentioned measurement error in at least one variable and specified at least one error mechanism ([Table 1](#)). Most mentioned independent nondifferential (85%) misclassification. Over half mentioned dependent error. The majority used "independent" or "dependent" to specify error type. Additional terms included "common-method bias," "same-source bias," and "interdependency." Some described independence without explicit term usage.

Articles commonly highlighted exposure (92%) or outcome measurement error (79%). Confounder measurement error

Table 1
Mentions of measurement error among the random sample (by journal type) and the citation-based sample of published articles from 2015 to 2016

Measurement error mentions	Random sample*						Citation-based sample [†]	
	Epidemiology journals [‡]		Medical journals [‡]		Random sample total			
	(n = 59)		(n = 41)		(n = 100)		(n = 39)	
	n	%	n	%	n	%	n	%
Any mention of potential for measurement error	51	86%	26	63%	77	77%	39	100%
Types of error/misclassification mentioned [§]	—	—	—	—	—	—	—	—
Clear mechanism identified	—	—	—	—	—	—	—	—
Yes	35	69%	20	77%	55	71%	39	100%
No—just general error mention	16	31%	6	23%	22	29%	0	0%
Dependent error/misclassification	—	—	—	—	—	—	—	—
Yes	0	0%	0	0%	0	0%	23	59%
Possible	0	0%	1	4%	1	1%	0	0%
No	51	100%	25	96%	76	99%	16	41%
Independent nondifferential misclassification	—	—	—	—	—	—	—	—
Yes	35	69%	18	69%	53	69%	33	85%
No	16	31%	8	31%	24	31%	6	15%
Independent differential misclassification	—	—	—	—	—	—	—	—
Yes	16	31%	13	50%	29	38%	20	51%
No	35	69%	13	50%	48	62%	19	49%
Variable(s) considered as having potential error/misclassification [§]	—	—	—	—	—	—	—	—
Exposure	—	—	—	—	—	—	—	—
Yes	42	82%	18	69%	60	78%	36	92%
No	9	18%	8	31%	17	22%	3	8%
Outcome	—	—	—	—	—	—	—	—
Yes	36	71%	18	69%	54	70%	31	79%
No	15	29%	8	31%	23	30%	8	21%
Confounder(s)	—	—	—	—	—	—	—	—
Yes	4	8%	3	12%	7	9%	6	15%
No	47	92%	23	88%	70	91%	33	85%
Evaluation of error's impact on measures of association	—	—	—	—	—	—	—	—
Discussion-based	39	76%	20	77%	59	77%	26	67%
Sensitivity analysis	11	22%	6	23%	17	22%	8	21%
Regression calibration	1	2%	0	0%	1	1%	0	0%
Quantitative bias analysis	0	0%	0	0%	0	0%	5	12%

* Random sample of 100 published articles from 2015 to 2016.

† Articles citing one of two prominent dependent misclassification articles (n = 39).

‡ Epidemiology journals: American Journal of Epidemiology (n = 29), Epidemiology (n = 12), and International Journal of Epidemiology (n = 18); Medical journals: British Medical Journals (n = 19), Journal of the American Medical Association (n = 8), The Lancet (n = 3), and The New England Journal of Medicine (n = 11).

§ Not mutually exclusive.

|| No quantitative evaluation (sensitivity analysis, calibration or bias analysis) reported in results, discussion, or supplements.

concerns were rare (15%). When dependent error was discussed, articles often focused on high error in exposure measurement, with cursory mention the error could be dependent on outcome error. Several articles appeared to confuse independent differential misclassification of exposure with exposure-outcome dependent misclassification. Exposure-confounder dependent error was never mentioned.

Mismeasurement concerns were commonly addressed in discussion sections and evaluation was typically qualitative (67%). Although less common, sensitivity analyses (21%) and quantitative bias analyses (12%) were used in some studies.

In our independent evaluation, likelihood for exposure-outcome dependent error in this citation-based sample was determined to be more common than in the random sample. Although exposure-

Table 2
Qualitative evaluation of likelihood for exposure-outcome and exposure-confounder dependent error stratified by study characteristics among the random sample of 100 published articles from 2015 to 2016

	n	Exposure-outcome dependent error						Exposure-confounder dependent error					
		Unlikely		Plausible		Probable		Unlikely		Plausible		Probable	
		n	%	n	%	n	%	n	%	n	%	n	%
All journals	100	85	85%	13	13%	2	2%	62	62%	23	23%	15	15%
Journal type	—	—	—	—	—	—	—	—	—	—	—	—	—
Epidemiology journals [†]	59	51	86%	7	12%	1	2%	33	56%	15	25%	11	19%
Medical journals [†]	41	34	83%	6	15%	1	2%	29	71%	8	20%	4	10%
Data collection	—	—	—	—	—	—	—	—	—	—	—	—	—
Cross-sectional	11	8	73%	2	18%	1	9%	5	45%	4	36%	2	18%
Retrospective	7	6	86%	1	14%	0	0%	3	43%	2	29%	2	29%
Prospective	80	69	86%	10	13%	1	1%	52	65%	17	21%	11	14%
Ambidirectional	2	2	100%	0	0%	0	0%	2	100%	0	0%	0	0%

† Epidemiology journals: American Journal of Epidemiology (n = 29), Epidemiology (n = 12) and International Journal of Epidemiology (n = 18); Medical journals: British Medical Journals (n = 19), Journal of the American Medical Association (n = 8), The Lancet (n = 3), The New England Journal of Medicine (n = 11).

Table 3
Qualitative evaluation of likelihood for exposure-outcome and exposure-confounder dependent error stratified by study characteristics among the citation-based sample of published articles ($n = 39$) from 2015 to 2016

	<i>n</i>	Exposure-outcome dependent error						Exposure-confounder dependent error					
		Unlikely		Plausible		Probable		Unlikely		Plausible		Probable	
		<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
All journals	39	21	54%	5	13%	13	33%	15	39%	13	33%	11	28%
Citation source	—	—	—	—	—	—	—	—	—	—	—	—	—
Brenner	11	7	64%	2	18%	2	18%	7	64%	1	9%	3	27%
Kristensen*	28	14	50%	3	11%	11	39%	8	29%	12	42%	8	29%
Data collection	—	—	—	—	—	—	—	—	—	—	—	—	—
Cross-sectional	20	5	25%	2	10%	13	65%	6	30%	7	35%	7	35%
Retrospective	5	5	100%	0	0%	0	0%	2	40%	3	60%	0	0%
Prospective	11	8	73%	3	27%	0	0%	6	55%	2	18%	3	27%
Ambidirectional	3	3	100%	0	0%	0	0%	1	33%	1	33%	1	33%

* One article cited both Kristensen and Brenner, but is only included in the Brenner sample.

outcome dependent error was considered unlikely for roughly half of articles, 33% were at probable risk (Table 3). Exposure-confounder dependent error likelihood was also common (28% probable; 33% plausible). Similar to the random sample, dependent error risk was often mitigated by separation of data collection (by timing and/or source) or by using objective variables with low possibility of error.

Discussion

Although many studies reviewed acknowledged mismeasurement as a bias source, thoughtful assessment of error mechanism and resulting biases were infrequent. Furthermore, most did not consider dependency of errors even when the study was likely susceptible. As expected, measurement error was more salient among studies citing prominent dependent error articles. Yet even in this citation-based sample, dependent error discussions were infrequent and sometimes confused with independent differential misclassification. Given our aim to obtain valid and precise measures of effect, measurement error represents an important validity threat similar to residual confounding or selection bias.

Many articles mentioning measurement concerns allotted only a few sentences to assessments. This finding is in line with prior reviews which found most measurement error discussions were cursory and nonquantitative [6–8]. Superficial assessments ignore important contributors to bias magnitude and direction [12], including the influence of random or systematic dependent error [9,13–15]. Although absence of detailed assessment may be due to many factors, simple quantitative bias methods exist [16]. As such, researchers need not rely on cursory assessments, assume little error, or focus solely on errors with expected biases toward the null.

Results suggest dependent error is not broadly acknowledged in spite of study susceptibility. Most articles reviewed, even those citing prominent dependent error articles, did not explicitly state whether errors were independent or dependent. Independence appeared presumed, although random or systematic dependence may occur [9,10,14,17]. Although exposures and outcomes were often separated in time and/or measurement method (reducing dependency concerns), exposures and confounders were frequently collected together. Particularly for measures with higher error rates, joint collection may increase exposure-confounder dependent error risk. Even measures commonly viewed as objective and valid (i.e., biomarkers) may be at risk when measured via the same medium, processed in the same laboratory, or analyzed via shared instrument [15]. Steps taken during design and data collection can reduce risk, particularly because dependent error bias analyses can be complex.

This review has several limitations. First, focus on observational research investigating exposure-outcome contrasts means results do not extend to randomized control trials and more descriptive studies. In addition, the random sample focused on high-impact journals which likely reject manuscripts with strong dependent error and the citation sample selected for articles focused on measurement issues. Given these factors, and general publication bias [18], results may not represent the true frequency of error mentions. We suspect error dependencies are more common yet similarly unacknowledged in the full published literature. Another limitation is reliance on qualitative assessment for dependent error risk. We took steps to increase rating consistency including having a review protocol, rules and examples for designations, and a second rater independently evaluate a subsample of articles. However, we cannot rule out measurement error in assessments. Finally, study details were limited to information in the article and supplements potentially missing details of error assessment conducted but not included in final publications.

This review has several strengths. First, a random sample was used to better represent the published literature. In addition, we reviewed a citation-based sample to explore how articles discussing dependent error addressed the issue. We also excluded methods-based articles. As such, results represent the focus and concerns of observational researchers. Although the review included a qualitative dependent error assessment, articles were reviewed multiple times for consistency and measurement error mentions were largely objective via direct article mentions. Finally, this research is novel. To our knowledge, it is the first to investigate the prevalence and content of measurement error mentions across a broad range of health-related topics with a focus on dependent error.

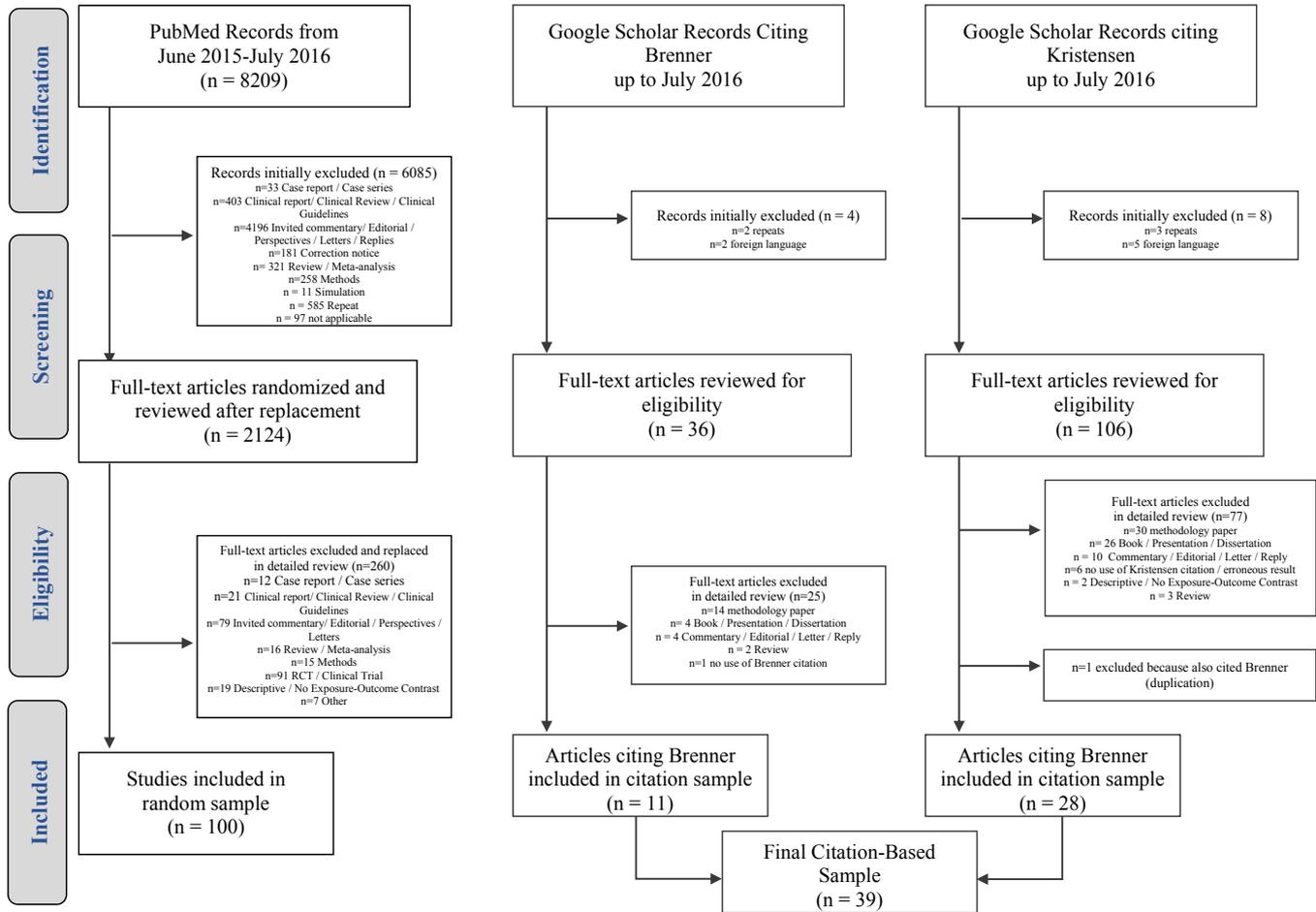
Results suggest mismeasurement and dependent errors in particular may not be top-of-mind for health researchers. Greater acknowledgment as a threat to validity and precision is needed. Researchers should work to limit dependent error via separation of data collection of variables in time and/or method. In addition, our results emphasize the need for more articles exploring the issue and methods for understanding resulting biases. In particular, more complex validation studies addressing both independent differential misclassification and dependent error are needed to help inform bias analyses. Finally, when dependent error remains a concern, researchers should acknowledge and evaluate the possible direction and magnitude of bias.

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Appendix



Supplement Fig. 1. Sample selection for the random and citation-based sample.

Additional background on measurement error with a focus on dependent error

Although consideration of potential independent error is important when evaluating systematic error, the possibility of dependent error warrants exploration. For example, nondifferential misclassification (i.e., the probability individuals are misclassified for a given variable does not differ with respect to their true classification status for another variable) is often assumed to bias effect estimates toward the null despite numerous exceptions [1–4,19]. This assumption is particularly salient for nondifferential exposure misclassification (e.g., sensitivity and specificity of exposure classification is the same among diseased and nondiseased). One important exception is when the independent error assumption between two or more analytic variables is violated. Several studies have shown potential for substantial bias in effect estimates resulting from even small amounts of nondifferential but dependent misclassification between exposure and outcome [3,4,6,7], as well as exposure and confounders [8]. Such dependencies occur when the probability of error within one variable is correlated with the probability of error in a second (as opposed to the actual value

of the second), resulting in more persons being jointly misclassified or mismeasured on both variables than expected based on the probabilities of errors in the two variables on their own [3,4,20].

Studies may be at particular risk for dependent error when the same subjective data collection method is used for both variables (e.g., self-report), when data collection timing is the same or similar across both variables (e.g., cross-sectional studies), or when a single instrument or source is used for measurement of both variables (e.g., biologic sample or assay) [3,4,7,10]. For example, in an interview-based study of illegal drug use (exposure) and risk of unprotected sex (outcome), those reluctant to report drug use might also underreport unsafe sexual behaviors. In this example, joint underreporting would inflate the number of individuals recorded as not using illegal drugs (unexposed) and not partaking in unprotected sex (lacking outcome behavior). The increased size of this group could create a strong upward bias in effect estimates. Given the potential for strongly biased effect estimates with even small amounts of dependent error and the fact that correction during analysis through quantitative methods can be difficult to parameterize, research should be designed and conducted to reduce the likelihood of dependent errors.

Methods (additional information on sample selection and article abstraction)

High-Impact Journals, Random Sample: The journals included three epidemiology-focused journals (American Journal of Epidemiology, *Epidemiology* and *International Journal of Epidemiology*) as well as four medical journals (British Medical Journal, *Journal of the American Medical Association*, *The Lancet* and *The New England Journal of Medicine*). These journals were selected as they are at the forefront of the medical and epidemiologic literature.

Exclusion of nonprimary articles included methodology articles, invited commentaries, reviews, opinion pieces, clinical reports/updates, or other articles not relevant to the search results.

Full-text review exclusion criteria: met one of the initial exclusion criteria (nonprimary research article), was a randomized trial, did not describe results focused on a clear exposure-outcome relationship(s), had unavailable information (or lacked sufficient detail) on variable data collection, or if the article was a descriptive/review article or meta-analysis.

Full study abstraction details: For each study, the following details were abstracted: dates and country of data collection, study design, data collection timing (prospective: outcomes had not occurred at baseline, although exposure may or may not have occurred; retrospective: exposure occurred before outcome, but both occurred before investigation; ambidirectional: a mixture of

retrospective and prospective; cross-sectional: exposure and outcome recorded at the same time point), sample size, basic study population demographics, maximum study follow-up time, topic areas (two maximum), primary exposure-outcome association (noting any secondary/tertiary relationships), data collection method, and analytic definition for main analytic variables (exposure, outcome, and final adjusted model confounder(s)), measure of association reported (e.g., odds ratio, rate ratio, mean change per unit increase), and crude and adjusted association(s). Abstraction also included whether measurement error/misclassification was evaluated/discussed, error mechanisms (if any) mentioned (non-differential, differential, independent, and/or dependent), what variables mentions were pertaining to (exposure, outcome, and/or confounder(s)), location of assessment (introduction, methods, results, discussion, and/or supplement), and nature of the evaluation (discussion-based, sensitivity analysis, regression calibration, or quantitative bias analysis). For citation-based articles, the usage of the citation within the article was also recorded.

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