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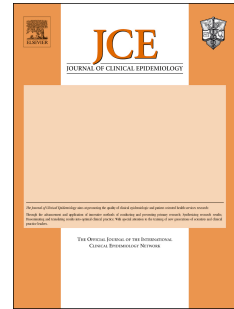
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# Accepted Manuscript

Measurement error is often neglected in medical literature: a systematic review

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1 **Measurement error is often neglected in medical literature: a systematic review**

2

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## 21 ABSTRACT

22 In medical research, covariates (e.g. exposure and confounder variables) are often measured  
23 with error. While it is well accepted that this introduces bias and imprecision in exposure-  
24 outcome relations, it is unclear to what extent such issues are currently considered in research  
25 practice. The objective was to study common practices regarding covariate measurement error  
26 via a systematic review of general medicine and epidemiology literature. Original research  
27 published in 2016 in 12 high impact journals was full-text searched for phrases relating to  
28 measurement error. Reporting of measurement error and methods to investigate or correct for  
29 it were quantified and characterized. 247 (44%) of the 565 original research publications  
30 reported on the presence of measurement error. 83% of these 247 did so with respect to the  
31 exposure and/or confounder variables. Only 18 publications (7% of 247) used methods to  
32 investigate or correct for measurement error. Consequently, it is difficult for readers to judge  
33 the robustness of presented results to the existence of measurement error in the majority of  
34 publications in high impact journals. Our systematic review highlights the need for increased  
35 awareness about the possible impact of covariate measurement error. Additionally, guidance  
36 on the use of measurement error correction methods is necessary.

37

38 **Key Words:** bias; epidemiology; measurement error; medicine; misclassification; review

39

40

## 41 WHAT'S NEW

- 42 • About half of the reviewed original research from 12 top-ranked general medicine and  
43 epidemiology journals mentioned the concept of measurement error in some form.
- 44 • Investigations into the impact of covariate (exposure and confounder) measurement  
45 error on studied relations as well as the application of measurement error correction  
46 methods were rare.
- 47 • This extensive systematic review confirms suspicions raised over a decade ago by  
48 many authors as well as another review on a similar topic: that the potential impact of  
49 measurement error on studied relations is often ignored and misunderstood.
- 50 • Consequently, it is difficult for readers to judge the robustness of presented results to  
51 the existence of measurement error in the majority of publications in high impact  
52 journals.
- 53 • Our systematic review highlights the need for both, increased awareness about the  
54 possible impact of covariate measurement error, as well as guidance on the use of  
55 measurement error correction methods.

56

## 57 1. Introduction

58 Measurement error is one of many key challenges to making valid inferences in biomedical  
59 research [1]. Errors in measurements can arise due to inaccuracy or imprecision of  
60 measurement instruments, data coding errors, self-reporting, or single measurements of  
61 variable longitudinal processes, such as biomarkers. With the increased use of data not  
62 originally intended for research, such as routine care data, ‘claims’ databases and other  
63 sources of ‘big data’, it is conceivable that measurement error is becoming increasingly  
64 prevalent in this field [2].

65  
66 It is generally well accepted that measurement error and classification error (hereinafter  
67 collectively referred to as measurement error) in either the dependent variable (hereinafter  
68 *outcome*) or independent explanatory variables (hereinafter *covariates*; e.g. exposure and  
69 confounder variables) can introduce bias and imprecision to estimates of covariate-outcome  
70 relations. Among others, several textbooks [3–6], methodological reviews [7,8] and a tool-kit  
71 [9], have demonstrated how to examine, quantify, and correct for measurement error in a  
72 variety of settings encountered in epidemiology. Most of this work has been focused on  
73 measurement error in covariates given its conceived greater impact on studied relations than  
74 measurement error in the outcome [4]. Despite these resources, it is suspected that the  
75 attention it receives in applied medical and epidemiological studies is insufficient [10,11].

76  
77 Over a decade ago, a review of 57 randomly selected publications from three high ranking  
78 epidemiology journals reported that 61% of the reviewed publications recognized the  
79 potential influence of measurement error, but only 28% made a qualitative assessment of its  
80 impact on their results, and only one quantified its potential impact on results [12]. In light of  
81 the increasing prevalence of measurement error in medical and epidemiological research and

82 increasing availability of methods and software to account for measurement error, a new and  
83 more comprehensive investigation into current practice is necessary.

84

85 We conducted a systematic review to quantify the extent to which (possible) measurement  
86 error in covariates is addressed in recent medical and epidemiologic research published in  
87 high impact journals. To guide the understanding of the results of the review, we briefly  
88 introduce key concepts in the field of measurement error.

89

## 90 **2. Measurement error**

91 Many variables of interest in medical research are subject to measurement error. Instead of an  
92 error-free and unobserved, *true* value of a variable, researchers have to deal with an  
93 imperfectly measured, *observed* value. For the remainder of this section, we consider the  
94 erroneous measurement and perfect measurement of a single underlying entity as different  
95 variables. Examples of variables prone to measurement error include the long-term average  
96 level of a variable biological process (such as blood pressure) when the researcher may only  
97 have access to a single measurement; average daily caloric intake measured using food  
98 frequency questionnaires; diabetic status ascertained using electronic health record data; and  
99 individual air pollution exposure based on measurements from a fixed monitor.

100

101 In the context of multivariable statistical models, such as regression models, measurement  
102 error can be present in the outcome and/or covariates. We focus on error in covariates. In their  
103 seminal text-book, Carroll et al. [5] describe the effect of measurement error in covariates as a  
104 “triple whammy”: covariate-outcome relationships can be biased, power to detect clinically  
105 meaningful relationships is diminished, and features of the data can be masked. Whether bias  
106 is present, and if so its direction and magnitude, depend on the form of the measurement

107 error. It is therefore important to quantify any bias due to measurement error and to obtain  
108 corrected estimates where possible. Three important considerations in this process are:  
109 identification of the variables of interest that are measured with error, what type of  
110 measurement error is present, and what additional information is available to help characterize  
111 the error.

112

### 113 *2.1 Types of measurement error and their effects*

114 Measurement error is characterized differently for continuous and categorical variables. For  
115 continuous variables, four types of error can be distinguished that describe how the observed  
116 variable relates to the unobserved, true variable.

117

118 The simplest type of measurement error, *classical* error, occurs when the observed variable  
119 can be expressed as the true variable plus a random component with zero mean and constant  
120 variance. As a result, when measurements of an observed variable (e.g. blood pressure) are  
121 repeatedly taken from the same person, the average of these measurements would approach  
122 that person's true variable value (e.g. the usual blood pressure level) as the number of  
123 replicate measurements increases. In the context of etiologic research, the estimated exposure-  
124 outcome relation will be biased towards the null (also known as attenuation) when only the  
125 exposure variable is measured with classical error [5]. However, the estimated relations  
126 between the confounders (provided that they are measured without error) and the outcome in  
127 the same model could be biased in either direction, depending on the form of the relation  
128 between the main exposure and the confounders. It follows that classical measurement error  
129 in one or multiple confounders can result in bias in either direction for the exposure-outcome  
130 relation, even if the exposure is measured without error [13]. The direction and magnitude of



131 this bias is thus unpredictable and this holds for different regression models of interest in  
132 epidemiology, including logistic, Cox and linear regression models [5].

133

134 Two other types of error that are related to the classical error model are *systematic* and  
135 *differential* error. When the error is systematic, the observed variable is a biased  
136 representation of the true variable and the average of repeated observed measurements would  
137 no longer approach the true variable value. Measurement error is described as ‘differential’ if  
138 the mismeasured covariate would help predict the studied outcome even if the values on the  
139 true covariate would have been observed (i.e., the error is dependent on the outcome,  
140 conditional on the values of the true covariate). Differential error depending on the outcome  
141 can arise when the outcome occurs prior to the measurement of covariates, as in case-control  
142 studies. Both systematic and differential error can cause bias in the exposure-outcome, or  
143 more generic, the covariate-outcome relation in either direction.

144

145 The last common type of measurement error is called *Berkson* error, which arises when the  
146 true variable is equal to the observed variable plus a random component with zero mean and  
147 constant variance; i.e. the true and observed variable reverse roles, compared to classical  
148 error. Berkson error can occur when group averages are used in place of individual  
149 measurements. Examples of Berkson error are often found in environmental epidemiology  
150 where individual exposure to air pollutants is set equal for individuals that live within a  
151 certain radius of an air pollution monitor. While Berkson error in covariates can diminish  
152 precision, in many cases it does not cause bias in the estimates of the exposure-outcome  
153 relation [5,14].

154

155 For categorical variables, measurement error is commonly referred to as *misclassification*.  
156 Misclassification can be summarized using sensitivity and specificity when the variable is  
157 binary. In the situation where a single binary exposure is related to an outcome, random non-  
158 differential misclassification present in the exposure will result in attenuation of this  
159 exposure-outcome relation [1]. However, when the exposure has more than two categories,  
160 when the exposure is subject to systematic or differential misclassification, or when  
161 confounders measured with error are added to the analysis model, it is once more difficult to  
162 predict in which direction the estimate of the true exposure-outcome relation will be biased  
163 [4].

164

## 165 *2.2 Measurement error correction methods*

166 Several methods have been proposed that aim to correct for bias due to measurement error in  
167 covariates. We highlight a few measurement error correction methods below that can be used  
168 when continuous variables are measured with error. The methodological literature addressing  
169 measurement error corrections is extensive, e.g. [1,4,5,14].

170

171 Regression calibration was proposed by Rosner, Willett and Spiegelman in 1989 [15]. The  
172 essence of regression calibration is that the observed error-prone covariate is replaced by a  
173 prediction of the expected value of the true variable in the analysis. Regression calibration can  
174 be used when there is non-differential classical or systematic measurement error. This  
175 approach requires information on the degree of measurement error, which is the error variance  
176 in the case of classical error. We note how this information can be obtained below.

177

178 Cook and Stefanski proposed the simulation-extrapolation (SIMEX) method [16]. This  
179 method works via a two-step procedure. First, data are simulated by adding additional error of

180 different magnitudes to the observed exposure measurements; the simulated data sets are used  
181 to estimate the effect of this additional error on the exposure-outcome relation. As a second  
182 step, the estimate of the exposure-outcome relation is extrapolated back to the situation where  
183 there is no measurement error using an extrapolation model which relates the estimated  
184 exposure-outcome association parameter to the degree of measurement error. Like regression  
185 calibration, this method requires information about the amount of measurement error  
186 (variance) in the observed variable. SIMEX as described above assumes non-differential  
187 classical error, yet has also been extended to deal with misclassified categorical variables  
188 [17].

189  
190 Alternatively, a large range of so-called latent variable models have been suggested to  
191 account for measurement error during analysis. Latent variable models generally rely on  
192 replicate measurements of error-prone measures to estimate a latent variable to represent the  
193 true error-free variable [18]. This latent variable can replace the observed error-prone variable  
194 in the exposure-outcome analysis or can be modelled directly in the exposure-outcome model,  
195 for instance, using Structural Equation Modeling [18,19].

196  
197 We acknowledge that it can be very challenging to determine the structure and amount of  
198 measurement error due to the plethora of underlying (unobserved) factors that may influence  
199 it. While further guidance is required on how to assess the amount and type of measurement  
200 error in practice, it can generally be recommended to collect additional data, whenever  
201 feasible, either in a subset of the study sample or possibly in an external validation sample, to  
202 compare observations on a covariate that is (suspected of being) measured with error and an  
203 error free representation of that covariate (if such a 'gold standard' exists). This information  
204 can subsequently be used to study measurement error structures, amount of measurement

205 error, and to inform measurement error correction methods (e.g. regression calibration or  
206 SIMEX, among others), which allow for a measurement error corrected analysis on the whole  
207 study sample. Alternatively, when available, repeated measurements of a covariate measured  
208 with error can be used to quantify measurement error variance and allow for measurement  
209 error corrected analyses.

210

### 211 *2.3 Availability of additional information for measurement error corrections*

212 Additional information about the form of the measurement error is often required to quantify  
213 its impact on the exposure-outcome relation and potentially correct for it. This information  
214 can be obtained from validation data or, if the error is classical, replicate measurements.

215

216 Validation data contains the error-prone variable alongside the true variable. Typically, these  
217 data are only available for a subset of the study sample or the information may come from an  
218 external source, such as another data set or published results. For example, when participants  
219 of a study have been requested to self-report their BMI via an online questionnaire (the error-  
220 prone variable), a subset may have had their BMI measured according to a systematic  
221 protocol by a research assistant (the ‘true’ variable).

222

223 Replicate measurements may consist of multiple measurements with error from the same  
224 instrument (e.g. multiple measurements of blood pressure), or sometimes multiple  
225 measurements from different instruments that aim to measure the same true variable (e.g.  
226 multiple diagnostic tests for the same disease). Replicates may be observed for all or a subset  
227 of study participants and is often collected when measuring a variable biological process.

228

229 When validation or replication data are acquired from external sources, the similarity of these  
230 research settings with the current setting, i.e., *transportability*, needs to be assessed [5].

231

232 If there is little information available to inform measurement error correction methods or to  
233 assess the structure of the measurement error model, the potential impact of measurement  
234 error can still be explored through sensitivity analyses. Hypothetical scenarios can then be  
235 assessed by rerunning the analysis assuming fixed amounts of measurement error or  
236 misclassification. A formal extension of sensitivity analysis, referred to as “probabilistic  
237 sensitivity analysis” (thoroughly detailed by Greenland & Lash in chapter 19 of [1]) can also  
238 be used to assess many potential scenarios with differing amounts of measurement error  
239 simultaneously, and obtain an estimate of the exposure-outcome relation adjusted for both  
240 systematic and random errors.

241

### 242 3. Methods

243 We performed a systematic review of original research published in 2016 in high-impact  
244 medical and epidemiological journals. Our aims were to: i) quantify and characterize the  
245 reporting of measurement error in a main exposure and/or confounder variables and their  
246 possible impact on study results and ii) quantify and characterize the use of available methods  
247 for investigating or correcting for measurement error in the exposure and/or confounder  
248 variables.

249  
250 Using the Thomson Reuters InCites rankings of 2015 [20], the 6 highest-ranking journals in  
251 the categories “General & Internal Medicine” (New England Journal of Medicine, Lancet,  
252 JAMA, BMJ, Annals of Internal Medicine and JAMA Internal Medicine) and  
253 “Epidemiology” (International Journal of Epidemiology, European Journal of Epidemiology,  
254 Epidemiology, American Journal of Epidemiology, Journal of Clinical Epidemiology, Journal  
255 of Epidemiology and Community Health) were identified. The journal Epidemiology Review  
256 was excluded as it is an annual journal. All publications of the above-mentioned journals from  
257 the period 01/01/2016 to 31/12/2016 were identified using PubMed (see search string in  
258 Appendix A).

259  
260 Title and abstracts were screened by one reviewer (TB). Publications that were not original  
261 research (e.g. brief reports, essays, cohort profiles, and guidance papers) were excluded. Also  
262 excluded were: methodological research, review and meta-analysis research, qualitative  
263 research, policy oriented studies, descriptive studies, studies that analyzed data on an  
264 aggregated level, and publications that did not assess individual health related exposures and  
265 outcomes.

266

267 After initial screening, a full-text search was performed in the remaining manuscripts using a  
268 Boolean search with stemming in Adobe Acrobat XI Pro. The search string contained the  
269 term “measurement error” and synonyms such as “misclassification” or “mismeasured”, as  
270 well as phrases relating to the validity of the collected data, including “information bias” or  
271 “self-reported”. The exact search string can be found in Appendix B. Manuscripts that  
272 contained any of the terms included in the search string were screened to assess whether they:  
273 a) discussed measurement error with respect to previous studies or the design of the current  
274 study; b) discussed the potential of measurement error in one or more of the covariates; c)  
275 discussed the potential effect of measurement error on the presented study results; or d)  
276 described methodology to investigate or correct for any measurement error. Publications that  
277 fulfilled at least one of these criteria were included in the following data extraction step.

278  
279 The included publications were reviewed independently by two readers (TB and MM) using a  
280 standardized data extraction form (see Appendix C). This form was pilot tested by four  
281 researchers (TB, MS, RG, MM). Disagreements were discussed until consensus was reached.  
282 The elements extracted included: design of data collection, study characteristics, clinical  
283 domain, characterization of variable(s) subject to measurement error (exposure/confounder),  
284 sections of the article where measurement error was mentioned  
285 (abstract/introduction/methods/results/discussion), reporting of possible effects of  
286 measurement error on study results (direction and magnitude of effect), reporting of the  
287 assumed type of error, reporting of methods that investigated the impact of, or attempted to  
288 correct for, measurement error in exposure or confounder variables.

289  
290 Articles that reported impact of measurement error or corrections for measurement error were  
291 included for additional review by four readers (TB, MS, RG, MM). For these publications,

292 data were extracted from the main document and the supplementary materials. The methods  
293 used were characterized, alongside how this was reported and the type of additional  
294 information used.

295

#### 296 **4. Results**

297 Figure 1 depicts the number of included papers at each step of the review process. Of the  
298 1178 articles found in PubMed, 565 (337 from Epidemiology journals and 228 from General  
299 & Internal Medicine journals) were judged as original research satisfying our inclusion  
300 criteria. Of these, 247 (44%) directly addressed measurement error in some form.  
301 Characteristics of these included studies are found in Table 1. Eighteen of these publications  
302 (3% of the 565) investigated the possible impact of, or corrected for, measurement error.  
303 Thirteen of these eighteen publications were from Epidemiology journals (4% of the 337  
304 Epidemiology publications) and the remaining five were from General & Internal Medicine  
305 Journals (2% of the 228 General & Internal Medicine publications). Table 2 shows from  
306 which journals the publications that directly addressed measurement error originated.

307

308

309 >> **insert Fig. 1** Flow Diagram Detailing the Systematic Review Process<<

310



311 >> **insert Table 1** General Characteristics of the 247 Publications That Explicitly Report on  
312 Measurement Error (ME) in Some Form.<<<

313

314 ME = Measurement error

315 <sup>a</sup> 174 (70%) publications considered ME **only** in the discussion section

316 <sup>b</sup> Mentions made of ME pertained to previously published research and not to the study presented in the  
317 published paper.

318 <sup>c</sup> ME in the presented study was prevented due to decisions made during the design of the study.

319

320

321

322

323

324

325

326 >> **Insert Table 2** In Which Journals the 247 Publications That Reported on Measurement  
327 Error (ME) and That Investigated or Corrected for it Were Published.<<

328  
329 ME=Measurement error

330  
331  
332

#### 333 *4.1 Measurement error in main exposure variables*

334 A total of 195 (79%) of the 247 publications reported on (possible) measurement error in the  
335 main exposure variable. Of these 195, 89 (46%) reported the presence of measurement error  
336 in the exposure but did not mention, or were unclear about, its possible effect on the studied  
337 relations; 66 (34%) reported that the measurement error in the exposure did or could have led  
338 to underestimation of the exposure–outcome relation; 25 (13%) reported that measurement  
339 error in the exposure was anticipated to have had no or a negligible effect on the estimated  
340 exposure-outcome relation; three (2%) publications stated that measurement error in the  
341 exposure could have led to both over- or underestimation of the studied effect; and one  
342 publication reported a possible overestimation of the exposure–outcome relation. 11 (6%)  
343 publications explicitly reported that their exposure variable was measured *without* error.

344

345 Information about the nature of measurement error was reported by 59 (30%) of the 195  
346 publications. For instance, these papers made general statements about the structure of the  
347 measurement error (e.g. using terms such as “random error” or “differential error”) or  
348 provided details on possible dependence of the measurement error on other variables in the  
349 analysis. Four publications (3%) were specific about the assumed error model; one  
350 publication assumed the error to be of the Berkson type and the remaining three investigated  
351 the form of the measurement error.

352

#### 353 *4.2 Measurement error in confounder variables*

354 Of the 44 publications that reported on measurement error in the confounders, 29 (66%)  
355 reported the presence of measurement error without mentioning (or were unclear about) its  
356 possible effect on the studied relations, six (14%) reported that the measurement error in the  
357 confounder did or could have led to underestimation of the relation between the main  
358 exposure and the outcome, and four (9%) reported that measurement error in the confounder  
359 was anticipated to have no or only a negligible effect on the main exposure–outcome relation.  
360 None of the publications reported on possible overestimation of the main exposure-outcome  
361 relation due to confounders measured with error. Five (11%) publications explicitly reported  
362 that their confounder variable(s) were measured *without* error.  
363 Six (14%) of the 44 publications made general statements about the structure of the  
364 measurement error. One discussed the assumed error model.

365

#### 366 *4.3 Measurement error impact and correction*

367 Of the 247 publications that directly reported on measurement error, 18 (7%) either  
368 investigated its impact on the studied relations or corrected the exposure-outcome relation for  
369 measurement error (Table 3).

370

371

372 >> **Insert Table 3** Characteristics of the 18 Publications That Reported on Investigation of or  
373 Correction for Measurement Error (ME).<<

374

375 ME=Measurement error

376 \*Methods designed specifically for a field of applied research

377

378 Seven publications (39%) of the 18, applied measurement error correction methods. Two  
379 publications used regression calibration, relying on internal validation data. One of these [21]  
380 used additional data gathered for a subset of participants to account for measurement error in  
381 the exposure (daily coffee intake). The other [22] corrected for measurement error in several

382 anthropomorphic measurements using data from earlier validation studies conducted within  
383 the same cohort. One publication [23] used a non-parametric method [24] to correct for  
384 underestimation of the exposure-outcome relation because of assumed random measurement  
385 error in the exposure (plasma triglycerides values at baseline). Another publication [25] used  
386 external observed air quality monitoring data to correct their estimates of individual air  
387 pollutant exposure. Two publications used factor analysis to define a latent exposure. One  
388 [26] implemented a latent variable model to determine each individual's disability score using  
389 many different items of a conceptual framework for describing functioning and disability.  
390 This score was then used in a regression analysis. In another [27] the factor analysis was  
391 embedded in a structural equation model where latent PTSD status was estimated from  
392 multiple clusters of symptoms suggestive of PTSD. Finally, Leslie et al. [28] used an ad-hoc  
393 approach, coined 'least significant change', to take into account inherent instrument  
394 measurement error when ascertaining exposure status (absolute bone mineral density  
395 difference).

396  
397 The remaining 11 (61%) of the 18 publications investigated the impact of measurement error  
398 on the exposure-outcome relation using sensitivity analyses. In five publications [29–33], an  
399 assumption was made about the amount of possible measurement error and its effect on the  
400 exposure-outcome relation was quantified. Often this was achieved by looking at a subgroup  
401 of the original sample for which the mismeasured variable of interest was assumed to be  
402 measured with less or no error. Four publications [34–37] looked at multiple scenarios in  
403 which they assumed different amounts of measurement error. The remaining two publications  
404 [38,39] performed a probabilistic sensitivity analysis. All authors reported that the results of  
405 the sensitivity analyses were either similar to those of the conventional analyses or did not

406 influence their conclusions. No study investigated the impact of measurement error on their  
407 results using an external dataset.

408

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ACCEPTED MANUSCRIPT

**413 5. Discussion**

414 This review provides an overview of the attention given to measurement error in recent  
415 epidemiological and medical literature. We found that a high proportion (44%) reported on  
416 the (possible) presence of measurement error in one or more recorded variables. 70% of these  
417 addressed measurement error in a qualitative manner only in the discussion section. In  
418 contrast, few publications (7%) used some form of measurement error analysis to investigate  
419 or correct the exposure-outcome relation for the presence of measurement error in covariates.

420  
421 The results of our review can be compared to the 2006 review by Jurek et al. [12]. In their  
422 review of 57 papers published in 2001 in 3 high impact epidemiology journals (American  
423 Journal of Epidemiology, Epidemiology and the International Journal of Epidemiology), the  
424 authors reported that 61% discussed measurement error in exposure variables in some form.  
425 Based on the 565 original research publications included in our review, we found the attention  
426 given to exposure measurement error in 2016 to be lower (35%). In both studies, roughly half  
427 of included papers did not report on the expected impact of measurement error on the studied  
428 relations (2001: 51% vs 2016: 46%), and the application of measurement error correction  
429 methods was found to be relatively rare (2001: 9% vs 2016: 3%). However, a marked  
430 difference was found in the proportion of papers reporting possible attenuation of the  
431 exposure-outcome relation due to measurement error (2001: 9% vs 2016: 34%). We note that  
432 the comparison between the reviews should be interpreted with some caution due to  
433 differences in the designs of the reviews. For instance, our review was based on a larger  
434 sample of publications, examined measurement error in confounder variables, and considered  
435 both “General & Internal Medicine” and “Epidemiology” journals.

436

437 Half of the 565 included publications in our study reported about measurement error being  
438 present in any of the studied variables. In our opinion, this proportion is quite high  
439 considering the denominator includes studies in which measurement error may not be an issue  
440 (e.g. clinical trials with objective endpoints such as mortality). As such, many authors  
441 justifiably ignored the issue and did not report on it in the final publication.

442  
443 As compared to the abundance of qualitative statements made about the presence of  
444 measurement error, we found formal measurement error evaluations to be surprisingly rare.  
445 About 4% of the papers that made a qualitative statement about measurement error quantified  
446 its impact using sensitivity analyses. Only 2% used formal measurement error correction  
447 methods. Several reasons for this low prevalence can be postulated. In practice it can be very  
448 challenging to properly assess the structure and amount of measurement error. Obviously,  
449 determining a strategy to account for measurement error in the analysis is then very difficult.  
450 But even when a suitable strategy can be determined and data are available to implement the  
451 strategy, there may still be lack of familiarity with these methods and available software  
452 among applied researchers, medical readers and journal editors, which may frustrate the  
453 adoption of these methods in the medical literature. For example, statistical software such as  
454 R [40] can be used to implement regression calibration (see supplementary material of [9]),  
455 SIMEX [41] and latent variable modeling [42]. There also seems to be a lack of educational  
456 materials and courses that provide guidance for practicing researchers, peer-reviewers and  
457 editors on how to use, assess and interpret results from measurement error correction  
458 methods.

459  
460 A need for better understanding of measurement error in medical and epidemiologic research  
461 is further supported by a noticeably high incidence (about one third of those that discussed

462 exposure measurement error) of manuscripts which claimed underestimation of the exposure-  
463 outcome relation due to measurement error. This conclusion was supported by a claim that the  
464 error was non-differential in about a third of the publications. Besides the fact that the non-  
465 differential measurement error assumption was regularly made without proof and is easily  
466 violated [14], non-differential measurement error also does not guarantee attenuation of the  
467 studied relation towards the null. As discussed in section 2, even classical (random) error can  
468 result in bias away from the null in several likely scenarios, e.g. when multiple variables in  
469 the analysis model are measured with error or when an exposure variable has more than two  
470 categories. In recent decades, several authors have attempted to dispel the myth that exposure  
471 measurement error always leads to attenuation of the studied relation [43–45].

472

473 Of the 18 publications that investigated or corrected for measurement error, most manuscripts  
474 reported both the original ('naïve') and the measurement error corrected results.  
475 Unfortunately, descriptions of the used methods were often not provided. Indeed, half of the  
476 publications that performed sensitivity analyses reported the results using only a single line in  
477 the results section claiming similarity of results to the main analysis (e.g., [36]). A similar  
478 proportion of these publications also only investigated one possible measurement error  
479 scenario.

480

481 Our review has some limitations. It cannot be ruled out that our full-text search strategy may  
482 have missed papers that mentioned measurement error. Although our search string covered a  
483 broad range of terminology related to measurement error, papers using atypical terms may  
484 have been overlooked. This might have led to an underestimation of the number of  
485 publications that discussed measurement error. This limitation is unlikely to have a substantial  
486 impact on the estimated percentages and conclusions, given that the intention was to give a



487 general impression of current practice of measurement error reporting. Second, in our review  
488 we ignored measurement error issues related to the outcome variable. While measurement  
489 error in outcome variables is often assumed to pose less problems than measurement error in  
490 covariates [4], we acknowledge that this choice limits our findings. Finally, there are  
491 measurement errors that influence analyses that do not strictly fall in the multivariable  
492 (exposure – outcome) classification. Specifically, diagnostic test accuracy studies often suffer  
493 from measurement error in the disease verification procedure, a problem known as “absence  
494 of gold standard”, and were outside the scope of this review. Reviews of methods [46,47] and  
495 the use of methods [48] to account for disease verification problems are found elsewhere.

496

497 Our systematic review also has strengths. By using modern, automated full-text searching  
498 capabilities in Adobe Reader, a comprehensive review could be conducted with about 10  
499 times as many included publications as the earlier review conducted by Jurek et al. [12] . We  
500 were able to consider all publications from 12 top-ranked journals for a full one-year period.  
501 This full-text searching approach is likely to be much more sensitive than common search  
502 strategies that are limited to wording in the title or abstract. In addition, the full-text procedure  
503 allowed us to systematically pinpoint the article section in which references to measurement  
504 error were made.

505

506 In conclusion, we found that measurement error is often discussed in high impact medical and  
507 epidemiologic literature. However, only a small portion proceeds to investigate or correct for  
508 measurement error. Renewed efforts are required to raise awareness among applied  
509 researchers that measurement error can have a large impact on estimated exposure-outcome  
510 relations and that tools are available to quantify this impact. More guidance and tutorials seem  
511 necessary to assist the applied researchers with the assessment of the type and amount of

512 measurement error as well as the steps that can subsequently be taken to minimize its impact  
513 on the studied relations. Given the unpredictable nature of the impact of measurement error  
514 on the studied results, we advise authors to report on the potential presence of measurement  
515 error in recorded variables but exercise restraint when speculating about the magnitude and  
516 direction of its impact unless the appropriate analysis steps are taken to substantiate such  
517 claims. Also, we recommend authors to make more use of available correction methods and  
518 probabilistic sensitivity analyses to correct analyses for variables that were measured with  
519 error. Given the increasing use of data not originally intended for medical or epidemiological  
520 research, we anticipate that the use and understanding of measurement error analyses and  
521 corrections will become increasingly important in the near future.

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## 525 CONFLICT OF INTEREST

526 Conflicts of interest: none

527

ACCEPTED MANUSCRIPT

528

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- 657
- 658

**Table 1** General Characteristics of the 247 Publications That Explicitly Report on Measurement Error (ME) in Some Form.

Characteristic	No. of Studies	% of 247
ME in which variable		
Exposure	195	79
Confounder	44	18
Outcome	115	47
Exposure & Confounder	35	14
ME discussed in which section		
Abstract	8	3
Introduction	22	9
Methods	49	20
Results	9	4
Discussion <sup>a</sup>	219	89
ME in previous study <sup>b</sup>	88	36
ME prevented by design <sup>c</sup>	60	24

ME = Measurement error

<sup>a</sup> 174 (70%) publications considered ME **only** in the discussion section

<sup>b</sup> Mentions made of ME pertained to previously published research and not to the study presented in the published paper.

<sup>c</sup> ME in the presented study was prevented due to decisions made during the design of the study.

**Table 2** In Which Journals the 247 Publications That Reported on Measurement Error (ME) and That Investigated or Corrected for it Were Published.

Journal Name	Publications that reported on ME		Publications that investigated/corrected for ME (n=18)
	No.	% of 247	
Am J Epidemiol	60	24	2
Ann Intern Med	7	3	1
BMJ	30	12	1
Epidemiology	17	7	4
Eur J Epidemiol	23	9	2
Int J Epidemiol	50	20	4
J Clin Epidemiol	2	1	0
J Epidemiol Community Health	37	15	1
JAMA	2	1	1
JAMA Intern Med	16	6	2
Lancet	2	1	0
N Engl J Med	1	0.5	0

ME=Measurement error

**Table 3** Characteristics of the 18 Publications That Reported on Investigation of or Correction for Measurement Error (ME).

Characteristic	No. of Studies	% of 18
Study design		
Cohort	14	78
Case-control	4	22
Exposure field		
Lifestyle/Health (not nutrition)	9	50
Nutrition	1	6
Environment	3	17
Education	1	6
Medical intervention	4	22
ME in which variable		
Exposure	15	83
Continuous	6	
Categorical	9	
Confounder	1	6
Continuous	1	
Categorical	0	
Exposure & confounder	2	11
Both categorical	1	

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Continuous & categorical	1	
How was ME dealt with		
Regression calibration	2	11
Latent variable analysis	2	11
Application specific methods*	3	17
Sensitivity analysis	11	61

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ME=Measurement error

\*Methods designed specifically for a field of applied research

