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Quality of reporting of confounding remained suboptimal after the STROBE guideline

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Abstract

Objectives: Poor quality of reporting of confounding has been observed in observational studies prior the STrengthening the Reporting of Observational studies in Epidemiology (STROBE) statement, a reporting guideline for observational studies. We assessed whether the reporting of confounding improved after the STROBE statement.

Study Design and Setting: We searched MEDLINE for all articles about observational cohort and case–control studies on interventions with a hypothesized beneficial effect in five general medical and five epidemiologic journals published between January 2010 and December 2012. We abstracted data for the baseline period before the publication of the STROBE statement (January 2004–April 2007) from a prior study. Six relevant items related to confounding were scored for each article. A comparison of the median number of items reported in both periods was made.

Results: In total, 174 articles published before and 220 articles published after the STROBE statement were included. The median number reported items was similar before and after the publication of the STROBE statement [median, 4; interquartile range [IQR], 3–5 vs. median, 4; IQR, 3.75–5]. However, the distribution of the number of reported items shifted somewhat to the right ($P = 0.01$).

Conclusion: Although the quality of reporting of confounding improved in certain aspects, the overall quality remains suboptimal. © 2016 Elsevier Inc. All rights reserved.

Keywords: Guideline adherence; Confounding factors; Guidelines as topics; Publishing/standards; Editorial policies; Epidemiology

1. Introduction

There is a growing interest into widespread problems affecting the validity and reliability of published health care research [1–4]. Inadequate reporting is a widespread problem and has been frequently observed in publications of animal and other preclinical studies, observational studies, diagnostic studies, clinical prediction research, surveys and qualitative studies, and randomized trials [3]. Several studies indicate that it is often impossible to replicate studies, partly due to poor reporting [5–7]. Complete and transparent

reporting is necessary to enable readers to assess the reliability and validity of study findings. Although poor reporting may have some correlation with the risk of bias [8], the reporting quality of a study does not necessarily reflect the methodological quality of the study [9,10]. Hence, without adequate reporting, it is difficult or impossible to assess the strengths and weaknesses of the study and to replicate the study. Furthermore, inadequate reporting wastes the time and resources invested in the conduct of research [3].

Guidelines on the reporting of research can improve the quality of reporting, especially if those guidelines are supported and adopted by journals [11–13]. Several guidelines have been developed to improve the quality of reporting of studies, including CONSolidated Standards of Reporting Trials (CONSORT), STrengthening the Reporting of Observational studies in Epidemiology (STROBE), Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), Standards for Reporting of

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What is new?**Key findings**

- The quality of reporting of confounding remained suboptimal after the publication of the STrengthening the Reporting of Observational studies in Epidemiology (STROBE) statement.
- Journals that published the STROBE statement and included an endorsement of the STROBE guidelines in their author instructions did have a similar reporting quality as journals that did neither.

What this adds to what was known?

- Poor quality of reporting of confounding has been observed prior the publication of the STROBE statement; this study shows that the quality is still suboptimal several years after the STROBE statement.

What is the implication and what should change now?

- The reporting of confounding may be improved by better adherence to the STROBE guideline and by making current and future scientist more aware of the importance of adequate reporting of confounding. Better adherence to the reporting guideline may be accomplished by requiring authors to submit a checklist with sufficient text excerpted from the manuscript, instead of only page numbers, to explain how they accomplished all applicable items.

Diagnostic Accuracy (STARD), Animal Research: Reporting of In Vivo Experiments, Standards for Quality Improvement Reporting Excellence, and Consolidated Health Economic Evaluation Reporting Standards [14]. A comprehensive list of reporting guidelines can be found elsewhere (<http://www.equator-network.org/http://www.equator-network.org/>) [14]. The STROBE statement was developed to improve the reporting of observational studies and published in 2007 [15]. The adoption of this guideline differs per journal, although it seems intuitive to assume that more active endorsement would result in better reporting quality. Some journals actively endorse the use of the STROBE guideline and require the submission of the STROBE checklist (http://www.strobe-statement.org/fileadmin/Strobe/uploads/checklists/STROBE_checklist_v4_combined.pdf), such as The BMJ and recently PLOS Medicine [16,17], whereas other journals only endorse the use of the STROBE statement in their Instructions for

Authors (e.g., Lancet) or do not mention the STROBE statement at all (e.g., New England Journal of Medicine).

It is well known that observational studies are prone to confounding because interventions are often prescribed to patients based on the perceived risk of the outcome instead of randomly assigned as in randomized controlled trials [18,19]. Moreover, especially for preventive interventions, patients who initiate and adhere to the intervention of interest may be more health conscious, have a more healthy lifestyle, and may also adhere better to other preventive interventions [20,21].

Despite the vulnerability of observational studies to confounding, poor quality of reporting of confounding has previously been observed [22]. Included articles were published before the STROBE statement, and it was suggested that this statement, which was intended to improve the reporting of observational studies, could have a considerable impact on the reporting of confounding [22].

To enable an adequate assessment of the likelihood that a study is affected by unmeasured or residual confounding, several items should be reported and discussed. This is acknowledged by the designers of the STROBE statement, who included several items related to the reporting of confounding in the STROBE checklist: item 7 requires that all potential confounders are clearly defined; item 12 requires that all statistical methods, including those used to control for confounding are described; item 14a requires that characteristics of study participants and information on exposures and potential confounders are given; item 16 requires the reporting of unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision together with a clear description of the confounders that were adjusted for and why they were included. In addition, the following items which are more general statements related to bias may improve the reporting of confounding: item 9 requires that any efforts to address potential sources of bias are described in the method section, and item 19 requires that the limitation of the study is discussed, taking into account sources of potential bias or imprecision, thereby discussing both the directions as magnitude of any potential bias.

Because multiple items related to confounding are included in the STROBE statement, we were interested whether the reporting of confounding improved over time.

Our primary objective was to assess whether the reporting of confounding improved in articles after the publication of the STROBE statement compared with articles published before that statement. In secondary analyses, we evaluated whether reporting was better for journals that published the STROBE statement, endorsed the STROBE statement in their Instructions for Authors, and/or required the completion of the STROBE checklist when submitting an observational study. We hypothesized that the reporting of confounding would have been improved after publication of the STROBE guideline, especially in journals that endorsed the STROBE statement.

2. Methods

As we intended to make a comparison with articles published before and after the STROBE statement, similar methods were used as previously described [22]. We searched the MEDLINE database to find observational studies that were published from January 2010 through December 2012 in the same five epidemiologic journals and five general medical journals. The five epidemiologic journal included International Journal of Epidemiology, Epidemiology, Journal of Clinical Epidemiology, American Journal of Epidemiology, and Journal of Epidemiology and Community Health. The five general medical journals included New England Journal of Medicine, The Lancet, Journal of the American Medical Association, The BMJ, and Annals of Internal Medicine. Those journals were selected in the previous study based on their high-impact factor [22]. Of these, five journals published the STROBE statement (The Lancet, The BMJ, Annals of Internal Medicine, Epidemiology, and Journal of Clinical Epidemiology). Of the journals that published the STROBE statement, The Lancet, The BMJ, and Annals of Internal Medicine also refer to the STROBE statement in their Instructions for Authors, whereas none of the other journals did endorse the STROBE statement in their instructions to authors. The BMJ was the only included journal that required the completion of the STROBE checklist when submitting an observational study.

2.1. Data selection

The search strategy aimed at identifying observational cohort and case–control studies that evaluated a hypothesized beneficial (preventive) effect of an intervention on a clinical outcome. Hence, studies on adverse effects were excluded. We did not include randomized controlled trials, meta-analyses, letters, comments, editorials, studies in which the primary outcome (as indicated by the authors or the outcome mentioned in the abstract) was intermediate (e.g., cholesterol levels instead of cardiovascular disease), nonintervention studies (e.g., effect of weather on myocardial infarction incidence), before–after studies, or non-English studies.

The search strategy is listed in Appendix A at www.jclinepi.com. In studies with multiple outcomes, we assessed the reporting related to the primary outcome. We excluded studies for which the allocation of the exposure of interest was likely determined by a random process as mentioned in Section 2 or anywhere else in the article as confounding will likely not play a role in such studies. For example, we excluded a study in which dispensation of proprietary vs. generic formulations of antiretroviral therapy was not driven by patient characteristics, but by the availability of drugs, with an effort to maintain a given patient on the same formulation from month to month. This resulted in a natural experiment that was close to a randomized trial, with a small likelihood of confounding.

We exported retrieved citations to Refworks (ProQuest, Ann Arbor, Michigan). Title and abstract screening were performed including all possibly relevant evaluations for further review. The full text of all remaining studies was retrieved and reviewed for eligibility.

2.2. Data extraction

Details on a number of basic study characteristics and items related to reporting of confounding were independently extracted by two researchers (K.B.P. and N.N.W.). Disagreements were resolved by consensus. Basic study characteristics were journal type (general medical or epidemiologic), study design (cohort or case–control), publication year, whether the journal published the STROBE statement, type of intervention, and type of outcome. To facilitate a comparison with the previous assessment of reporting of confounding prior the publication of the STROBE statement [22], the same information on the design and analytical details concerning confounding were extracted (Table 1) [22]. It was assessed whether the following items were reported: characteristics of key confounders as well as reasons why potential confounders were selected for analysis and included in the final model; methods to control for confounding (e.g., stratification, multivariate regression, propensity score matching etc.); and both the crude as well as the adjusted effect estimate, in case only an adjusted effect estimate was reported, it was considered sufficient if the crude effect estimate could be calculated using data from the article. Furthermore, it was evaluated whether qualitative statements on the likelihood and direction of the potential impact of unmeasured confounders were reported. Finally, we assessed whether a quantitative sensitivity analysis to estimate the potential impact of unmeasured confounders on the effect estimate was included in the published article.

The original data from the previous study [22] were obtained to enable a comparison of a period before the STROBE statement was published (January 2004–April 2007; previous study) with the period after the STROBE statement (January 2010–December 2012; present study).

2.3. Comparisons and data analysis

In primary analysis, a comparison was made between the quality of reporting of confounding before vs. after the publication of the STROBE statement.

Three secondary analyses were performed. First, articles from journals that published the STROBE statement—used as an indicator that the journal acknowledges the importance of adequate reporting—(The Lancet, BMJ, Annals of Internal Medicine, Epidemiology, and Journal of Clinical Epidemiology) were compared with articles from journals that did not publish the STROBE statement (American Journal of Epidemiology, International Journal of Epidemiology, New England Journal of Medicine, Journal of the

Table 1. Frequencies of important items in the reporting of confounding in observational studies

| Item | Studies with adequate reporting (2004–2007, <i>n</i> = 174) (%) | Studies with adequate reporting (2010–2012, <i>n</i> = 220) (%) | RR (95% CI) |
|---|---|---|------------------|
| Reporting of reasons why potential confounders are selected for analysis | 18 (10.3) | 55 (25.0) | 2.42 (1.49–3.96) |
| Reporting of reasons to include confounders in the final model ^{a,b} | 88 (50.6) | 88 (40.0) | 0.79 (0.64–0.98) |
| Reporting of characteristics of key confounders ^c | 139 (79.9) | 175 (79.5) | 1.00 (0.90–1.11) |
| Reporting of any method used to control for confounding ^d | 171 (98.3) | 218 (99.1) | 1.01 (0.98–1.04) |
| Reporting of both crude and adjusted effect estimate ^b | 136 (78.2) | 160 (72.7) | 0.93 (0.83–1.04) |
| Comment on likelihood unmeasured confounding ^e | 102 (58.6) | 186 (84.5) | 1.44 (1.27–1.67) |
| Qualitative statement direction unmeasured confounding ^e | 27 (15.5) | 71 (32.2) | 2.08 (1.41–3.10) |
| Quantitative bias analysis for unmeasured confounding | 4 (2.3) | 8 (3.6) | 1.58 (0.52–4.88) |

Abbreviations: RR, relative risk; CI, confidence interval; STROBE, STrengthening the Reporting of Observational studies in Epidemiology.

^a STROBE item 7: clearly define all outcomes exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.

^b STROBE item 16(a): give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included.

^c STROBE item 14(a): give characteristics of study participants (e.g., demographic, clinical, social) and information on exposures and potential confounders; give information separately for cases and controls in case–control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

^d STROBE item 12(a): describe all statistical methods, including those used to control for confounding.

^e STROBE item 19: discuss limitation of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.

American Medical Association, and Journal of Epidemiology and Community Health).

Second, we compared journals that published the STROBE statement and included an endorsement of the STROBE guidelines in their author instructions (The Lancet, The BMJ, and Annals of Internal Medicine) with journals that did neither (American Journal of Epidemiology, International journal of Epidemiology, New England Journal of Medicine, Journal of the American Medical Association, and Journal of Epidemiology and Community Health).

Third, The BMJ, the only included journal that required the completion of the STROBE checklist when submitting an observational study, was compared with the two journals that only endorsed the STROBE statement in their author instructions (The Lancet and Annals of Internal Medicine). This was done to evaluate whether such more active endorsement of the STROBE statement would result in better reporting of confounding.

Our primary outcome consisted of the same eight-item score that was created and used previously, excluding items 1 and 8 from Table 1 that are not addressed by the STROBE statement [22]. Hence, a six-item score was created with equal weights given to each item. For the comparison of the overall quality of reporting, a comparison was made between the median number of reported items (maximum of 6) before and after the STROBE statement using the Mann–Whitney *U*-test. In addition, relative risks 95% confidence interval (CI) were calculated to represent changes in the individual items. Statistical analyses were performed using the R statistical software package version 3.0.2.

2.4. Sensitivity analysis

Of the eight items related to confounding that we considered important, two items are not included in the STROBE statement. The reason why potential confounders were selected for analyses and the application of a quantitative bias analysis are both not mentioned in that guideline. Therefore, in the primary analysis, we used a six-item score, excluding the two items that are not addressed by the STROBE statement. However, because both items are important for evaluating the likelihood and potential impact of unmeasured confounding [23–28], we performed a sensitivity analysis in which we used the same eight-item score that was created and used previously [8], including these two items.

3. Results

The MEDLINE search identified 2,651 publications (Fig. 1). After screening the titles and abstracts of all retrieved publications, we reviewed 408 full-text articles and subsequently included 220 articles in the final analysis (Appendix B at www.jclinepi.com). Of those studies, 125 (56.8%) were published in general medical journals and 95 (43.2%) in epidemiologic journals. Of the included articles, 66 were published in 2010, 75 in 2011, and 79 in 2012. There were more cohort studies (181, 82.3%) than case–control studies (39, 17.7%) included. Among general medical journals, only 11.2% of studies were case–control studies. Most studies were published in journals that did not

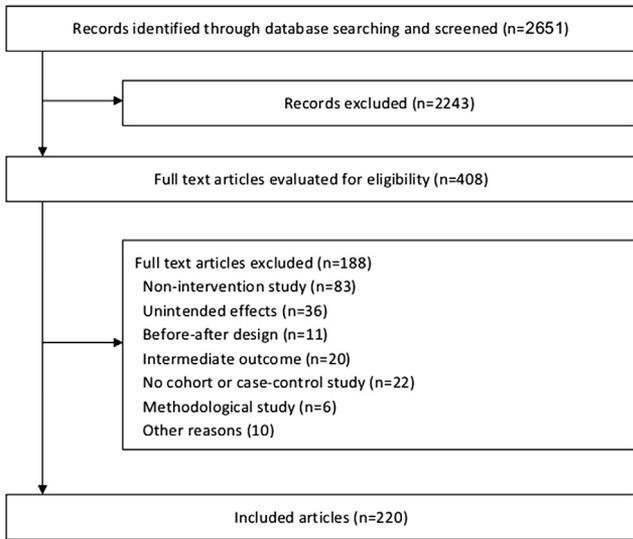


Fig. 1. Flow diagram for study selection.

publish the STROBE statement (151, 68.6%). In 72 articles (32.7%), the effects of diets were studied; in 52 (23.6%), the effects of drugs; in 24 (10.9%), the effects of surgical procedures; in 27 (12.3%), the effects of medical strategies (e.g., the association between mechanical ventilation and survival among patients with acute lung injury); 20 (9.1%) articles described the effects of behavioral interventions (e.g., the effect of physical activity on mortality); 12 (5.5%) reported the effects of vaccination; 7 (3.2%) the effects of screening or preventive measures, and 6 (2.7%) about other interventions such as hospital recognition of nursing excellence.

Table 1 shows the frequencies of items in the reporting of confounding in observational intervention studies. Low frequencies were observed for the reporting of reasons why

potential confounders were selected for analysis, the reporting of reasons to include confounders in the final model, reporting of comments on the direction of the potential effect of unmeasured confounding, and the use of sensitivity analysis to quantify this potential effect (Table 1). When interpreting these results, it should be noted that the reasons why potential confounders were selected for analysis and the use of sensitivity analysis to quantify the potential effect of unmeasured confounding are not included in the STROBE statement. Nevertheless, compared with the period before the STROBE statement, the reporting of reasons why potential confounders were selected for analysis improved. Other items that were more frequently reported were comments on the likelihood of unmeasured confounding, and qualitative statements about the direction unmeasured confounder(s) would likely bias the results (Table 1). However, reports included less frequently the reasons to include confounders in the final model. The other items did not change significantly.

The median number of items reported was similar before and after the publication of the STROBE statement [before: median, 4; interquartile range [IQR], 3–5; after: median, 4; IQR, 3.75–5]. However, the distribution of the number of items reported shifted somewhat to the right with less articles with a low number of items and more articles with a high number of items (Fig. 2, $P = 0.01$). When in sensitivity analysis, items 1 and 8 from Table 1 were included in the summary score, this shift became slightly stronger (median, 4; IQR, 3–5 vs. median, 4; IQR, 4–5; $P = 0.0007$).

When journals that published the STROBE statement in 2007—used as an indicator that the journal acknowledges the importance of adequate reporting—were compared with journals that did not, median number of items reported were not statistically significant higher for journals that published the STROBE statement (median, 4; IQR, 4–5 vs. median, 4; IQR, 3–5; $P = 0.26$). Similar results were

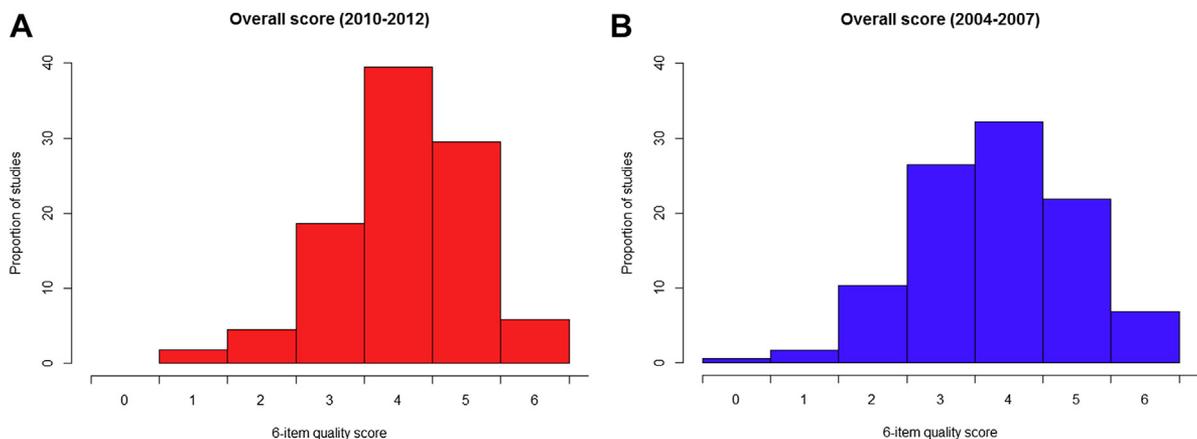


Fig. 2. Histograms of the overall scores for the quality of reporting of confounding. (B) Blue bars represent the proportion of studies with 0–6 items reported for studies published between January 2004 and April 2007. (A) Red bars represent the proportion of studies with 0–6 items reported for studies published between January 2010 and December 2012. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

obtained when comparing journals that published the STROBE statement and included an endorsement of the STROBE guidelines in their author instructions with journals that did neither (median, 4; IQR, 4–5 vs. median, 4; IQR, 3–5; $P = 0.33$). Articles from the BMJ, the only included journal that required the submission of a completed STROBE checklist, did not have a better reporting of confounding than journals that endorsed the STROBE statement in their author instructions but did not require the completion of the checklist (median, 4; IQR, 4–5 vs. median, 4; IQR, 3.5–5; $P = 0.72$).

4. Discussion

Although the quality of reporting of confounding in articles on observational interventions improved in certain aspects because the introduction of the STROBE statement, this study shows that the overall quality of reporting remains suboptimal.

Quantitative bias analyses were still very rare (reported in 3.6% of the articles), whereas such analyses can be very informative and potentially avoid unnecessary harm to patients and waste of time and resources invested in new research [22]. Despite the increasing number of articles in the literature emphasizing the importance of quantitative bias analysis [25,28–34], such analyses are still rarely applied as observed previously [22]. Although we acknowledge that there are situations where quantitative bias analysis may not be very useful, such as analyses with very wide conventional confidence intervals, we do think that the STROBE statement should ask authors to report on quantitative bias analysis or—if not conducted—report why not.

It is difficult to imagine that the current practice of systematically ignoring sources of uncertainty other than random error is the way forward. Especially with the increasing interest in and use of big data [35,36], very narrow confidence intervals can be expected. Without a quantitative bias analysis, researchers and decision makers risk largely underestimating the true uncertainty in these circumstances. In the future, reporting of quantitative bias analysis and the other items from our Table 1 enables a better assessment of the risk and impact of confounding using, for example, the currently developed “Cochrane risk of bias assessment tool for non-randomized studies of interventions” [37].

The reasons why potential confounders were selected for analysis and included in the final analysis were also frequently missing from the included articles. Reporting of both items is important, as causal inference from observational data depends not only on the data, but also on the design of the study and subject-specific knowledge [26–28]. Without a structured way to obtain subject matter knowledge, it will be difficult to define a causal structure, a prerequisite to adequately select a variable as a potential confounder [26–28]. Hernan et al. previously showed the importance of communicating which strategy is used to select the

confounders included in the final model [27]. Ideally, causal diagrams are used to summarize and communicate the causal structure assumed by the researchers. Of the articles in the 2010–2012 cohort, 0.9% included a causal diagram. Such diagrams may also enable the researcher to determine the direction of the bias caused by unmeasured confounding [38], another item that was frequently not reported.

Reporting of both crude and adjusted effect estimates remained similar. If both effect estimates are reported, readers can judge by how much, and in what direction, potential confounders changed the effect estimate [39]. Together with a distribution of the confounders among exposed and unexposed or cases and controls, this information can be used to understand the data behind the reported associations. Unfortunately, almost 20% of the included studies did not report the characteristics of all key confounders. Only the reasons why potential confounders are selected for analysis (item 1), comments on likelihood of unmeasured confounding (item 6), and qualitative statements about the direction of unmeasured confounding (item 7) were more frequently reported over time.

This is the first study that evaluated whether the reporting of confounding improved after the publication of the STROBE statement. Moreover, this is the first study that evaluated whether the reporting of confounding is better in journals with a more active endorsement of the STROBE guideline.

This study has some potential limitations. Although most evaluated items are included in the STROBE checklist, the application of a quantitative bias analysis and an item about the reason why potential confounders are selected for analysis are not mentioned in that guideline. Therefore, one may expect that these items would not increase substantially over time as a result of the STROBE statement. However, after including both items, the difference before and after the STROBE statement became larger instead of smaller, indicating that including these items would not result in an underestimation of the impact of the STROBE statement.

We focused on studies published in a selection of high-impact general medical and epidemiologic journals. Such high-impact general journals may have a better reporting quality than lower impact and specialist journals [40], resulting in an overestimate of the quality of reporting of confounding in all published studies on observational medical interventions.

The observational nature of the before–after comparison may have masked effects of the STROBE guideline, due to underlying trends. Because we were mainly interested in the question whether the reporting improved since the previous study that was performed prior the STROBE statement [22], we did not directly evaluate the impact of the STROBE statement [15], the launch of the EQUATOR Network and its activities [14], the previous study showing poor reporting of confounding in observational research [22], or other articles that showed the importance of adequate reporting or the

lack of adequate reporting in different journals [41–45] using for example a time-series analysis. For such an analysis, as done by Bastuji-Gain et al. [46], the potential lag time between implementation and effect would be ideally known, including other events and interventions happening in between plus the exact dates. Moreover, there was no trend seen in the previous study in the median number of items reported over time using data from 2004 to 2007 [22] nor in the years 2010 to 2012 (2010: 4; IQR, 4–5; 2011: 4; IQR, 3–5; 2012: 4; IQR, 4–5).

Our data are in agreement with previous studies that showed that especially the reporting of selection of confounders for analysis needs improvement [22,47–49]. Moreover, in agreement with other studies [22], key issues related to unobserved confounding are not addressed and/or underreported. Although there is evidence that reporting guidelines such as the CONSORT and STARD statement improve the completeness of reporting [50–52], the effect of the STROBE statement on the quality of reporting is less clear [44,46,52]. Despite we did find that the reporting of confounding improved slightly over time and was better after than before the STROBE statement was published, journals that published the STROBE statement or were more actively endorsing the STROBE statement did not have a statistically significant better reporting of confounding. This finding is in agreement with a recent systematic review that did not find a clear relationship between journals' endorsement of reporting guidelines (BMJ economic checklist, CONSORT for harms, PRISMA, QUOROM, STARD, STRICTA, and STROBE) and the completeness of reporting [52].

In conclusion, reporting of confounding in articles on observational interventions remained suboptimal. Although we acknowledge that improving the quality of reporting of confounding does not solve the whole problem of published research that cannot be replicated and for which it is unclear how reliable and valid the study findings are, there is still room and need for improvement. How such improvements should be accomplished remains a difficult issue. Publishing the STROBE statement or endorsing it in the instructions for authors does not seem to be enough. The recently implemented strategy of PLOS Medicine is an interesting solution [17]. Requiring authors to submit a checklist with sufficient text excerpted from the manuscript to explain how they accomplished all applicable items [17] may result in better adherence to the guideline. In addition, adequate reporting and knowledge about the existence of the different reporting guidelines listed on the EQUATOR network Web site should preferably become part of the core training of current and future scientists, to make them more aware of the importance of adequate reporting already at the beginning of their study. Furthermore, we would like to encourage research into the development and evaluation of strategies to improve the quality of reporting, thereby reducing the waste.

Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.jclinepi.2015.08.009>.

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