International Society for Evidence-Based Health Care
26th Newsletter Edition, 2019

Mission

The mission of the International Society for Evidence-Based Health Care is to develop and encourage research in evidence-based health care and to promote and provide professional and public education in the field.

Vision

The society is inspired by a vision to be a world-wide platform for interaction and collaboration among practitioners, teachers, researchers and the public to promote EBHC. The intent is to provide support to frontline clinicians making day-to-day decisions, and to those who have to develop curricula and teach EBHC.

Key objectives of the Society

- To develop and promote professional and public education regarding EBHC
- To develop, promote, and coordinate international programs through national/international collaboration
- To develop educational materials for facilitating workshops to promote EBHC
- To assist with and encourage EBHC-related programs when requested by an individual national/regional organization
- To advise and guide on fundraising skills in order that national foundations and societies are enabled to finance a greater level and range of activities
- To participate in, and promote programs for national, regional and international workshops regarding EBCP
- To foster the development of an international communications system for individuals and organizations working in EBHC-related areas
- To improve the evidence systems within which health care workers practice.

EBCP WORKSHOP

international society for EVIDENCE BASED HEALTH CARE

Evidence-Based Clinical Practice Office
McMaster University, Canada

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A Novel Approach to Evaluating the Plausibility of Causal Relationships from Non-randomized Studies

Dena Zeraatkar, Bradley C. Johnston

The presence of a dose-response gradient has long been recognized as an important criterion for evaluating putative causal relationships. GRADE, for example, suggests rating up the certainty of evidence if a dose-response gradient is observed (1). A dose-response gradient, however, may be less convincing of a causal relationship in scenarios in which the exposure of interest is highly correlated with other potentially confounding exposures. Nutritional exposures, for example, are highly correlated with one another (2).

When randomized trials are not feasible or when there is insufficient evidence from randomized trials, non-randomized studies can provide important information on relationships between exposures and health outcomes. In a series of systematic reviews addressing the association between red and processed meat consumption and adverse cardiometabolic and cancer health outcomes that informed the recently published NutriRECS guideline (3), we implemented a novel approach to evaluate the plausibility of causal inferences drawn from non-randomized studies.

In our systematic reviews, we observed a dose-response association between greater red meat intake and increases in a number of adverse cardiometabolic and cancer health outcomes (4, 5). Because the consumption of red meat is highly correlated with other dietary characteristics (e.g., sodium, alcohol), we undertook an additional systematic review to compare health outcomes associated with adherence to dietary patterns that are lower versus higher in red meat (6). We anticipated that if red meat is indeed a primary causal agent, the observed association between red meat and adverse health outcomes would be greater in studies directly addressing red meat compared to dietary pattern studies. This is because studies directly addressing red meat can examine a larger gradient in red meat intake (i.e., very low intake of red meat vs. very high intake of red meat) compared to dietary pattern studies in which participants are differentiated by their intake of a number of foods and nutrients, in addition to red meat, as a result of which the gradient in red meat intake is smaller (i.e., moderately low intake of red meat vs. moderately high intake of red meat).

We found effect estimates from our systematic review of studies addressing dietary patterns to be similar to those from our systematic review of studies on red meat, which suggests that the association between red meat and adverse health outcomes may be confounded by other foods and nutrients that are correlated with the consumption of red meat (Table 1). Given these findings, we did not feel sufficiently confident to rate up the evidence for dose-response.

Comparing the magnitude of association of highly correlated and potentially confounding exposures with the outcome of interest to the magnitude of association between the exposure and the outcome directly may be useful to evaluate the plausibility of causal relationships in fields where exposures are highly correlated, such as nutritional and lifestyle epidemiology (2). We caution investigators regarding rating up for dose-response in situations where the exposure of interest is highly correlated with other potentially confounding exposures.

Table 1: Plausibility of Causal Inferences Based on Summary of Evidence for Observed Effects for Red Meat, Processed Meat, and Dietary Patterns

Outcome	Unprocessed Red Meat *(reduction of 3 servings/week)*		Processed Meat *(reduction of 3 servings/week)*		Dietary Patterns *(lower vs. higher in red meat)*	
	Risk Difference	**Certainty of Evidence**	**Risk Difference**	**Certainty of Evidence**	**Risk Difference**	**Certainty of Evidence**
Cardiovascular mortality*†	4 fewer per 1000 persons (from 5 fewer to 4 fewer) over 10.8 y	⊕◯◯◯ VERY LOW	4 fewer per 1000 persons (from 7 fewer to 1 fewer) over 10.8 y	⊕◯◯◯ VERY LOW	6 fewer per 1000 persons (from 9 fewer to 2 fewer) over 10.8 y	⊕◯◯◯ VERY LOW
Type 2 diabetes*†	6 fewer per 1000 persons (from 7 fewer to 4 fewer) over 10.8 y	⊕⊕◯◯ LOW	12 fewer per 1000 persons (from 16 fewer to 9 fewer) over 10.8 y	⊕◯◯◯ VERY LOW	14 fewer per 1000 persons (from 18 fewer to 8 fewer) over 10.8 y	⊕◯◯◯ VERY LOW
Overall cancer mortality†‡	7 fewer per 1000 persons (from 9 fewer to 6 fewer) over lifetime	⊕⊕◯◯ LOW	8 fewer per 1000 persons (from 12 fewer to 6 fewer) over lifetime	⊕⊕◯◯ LOW	12 fewer per 1000 persons (from 18 fewer to 4 fewer) over lifetime	⊕◯◯◯ VERY LOW

* Based on reference 3. † Based on reference 5. ‡ Based on reference 4

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Does Framing by Surgeons Affect Patient Decision-making in Rotator Cuff Surgery? A Prospective Randomized Study

Carlos Torrens, Joan Miquel, Fernando Santana

Surgeons may place more emphasis on the benefits that may be obtained from a particular procedure, versus possible rate of failure, when speaking with their patients. Our group conducted a study to explore whether patient's decisions to undergo surgery was affected with how details on expected outcomes was presented. (1)

Patient's diagnosed with a rotator cuff tear were randomly allocated to group I (information given in a positive way) or to group II (information given in a negative way), and therefore had to answer one of the following questions depending on the assigned group:

Group I: Your doctor informs you that you have a rotator cuff tear and states that if he/she surgically repairs your cuff tear you will improve and that the cuff remains healed at the 2-year follow-up in 71% of the cases where surgery is done. Would you choose surgery? Yes or No

Group B: Your doctor informs you that you have a rotator cuff tear and that if he/she surgically repairs your cuff tear you will improve and that the cuff is torn again at 2-year follow-up in 29% of the cases where surgery is done. Would you choose surgery? Yes or No

80 patients participated in the study (43 in group I and 37 in group II). Patients in the positive/benefit group accepted surgery more often than those belonging to the negative/side-effect group ($p<0.001$). In group I, 84% of the patients accepted surgery compared to 46% in group II.

Patients informed in a positive/benefit-focussed way are more prone to accept surgery. The way that doctors deliver information affects patient's decision-making. Further studies are needed to inform optimal communication for shared-decision making, but surgeons should ensure that patients considering

surgery are aware of both the potential for benefit and failure. Patient satisfaction with surgical outcomes is often poor when expectations are not met.

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Multiplicity Considerations in Recent Thrombosis Related Clinical Trials

Samuel A. Berkman

Confirmatory (phase 3) randomized clinical trials are often designed with composite rather than single endpoints, with the aim of improving power to detect a statistically significant effect. Such trials also typically include multiple secondary endpoints, sometimes arranged hierarchically.

The more endpoints, both primary and secondary, the greater the likelihood for the occurrence of a false positive result, or a type one error. The purpose of adjustment for multiplicity is to minimize the likelihood of false positive results, and both the Food and Drug Administration and the European Medicine Agency have recently released guidelines on multiplicity.

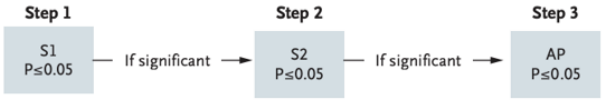
One example of multiplicity adjustment in thrombosis is illustrated in the recent Compass trial where aspirin (100mg per day) plus Rivaroxaban (2.5 mg bid) was compared to aspirin alone in patients who had preexisting coronary artery disease, 60% of whom had a previous myocardial infarction. The incidence of the primary composite end point of stroke, myocardial infarction and cardiovascular death, was 24% lower in the combination group, which was statistically significant. Mortality, on its own, showed an 18% reduction in the combination group versus the aspirin alone group at p=0.01; however after multiplicity adjustment using the Hochberg procedure, the mortality benefit was no longer deemed statistically significant, as it had to be less than 0.0025 to prevent false positive results.

Some experts view no need to correct for multiplicity and view such testing as somewhat arbitrary and particularly do not see why they should be applied to a trial like Compass, which was stopped early by the drug monitoring safety board. However other expert methodologists differ and feel the strict guidelines regarding the need for multiplicity adjustment being promulgated by the regulatory agencies are not occurring in a vacuum. As a compromise, the 18% reduction in mortality is presented with an asterisk in the Rivaroxaban package insert showing a p value and confidence interval indicating superiority in mortality, but with the asterisk denoting no adjustment for multiplicity.

The APEX trial provides another example regarding multiplicity adjustment in a recent thrombosis trial. This study compared factor Xa inhibitor Betrixaban with low-molecular-weight heparin in critically ill hospitalized patients during hospitalization and after discharge. Two different tests were used to check for multiplicity.

In a fixed sequence test (see figure 1)

FIGURE 1- FIXED SEQUENCE TEST IN APEX TRIAL



In the Apex trial subpopulation one(patients with D Dimer over 2 times the upper limit of normal) was tested first, then subpopulation two (the same as population one but also over 75 years old , then subpopulation three called AP for all comers . For the study to be viewed as successful in fixed sequence , step one has to achieve a a p value of under .05, which it did not at 0.054. Therefore with the fixed sequence test no matter what the p values achieved in subpopulations 2 (.03) and 3,(.006) the study is viewed to be only hypothesis generating in fixed sequence because subpopulation achieved 1 achieved a p value of 0.054 which was not under .05

Adapted from Dmitrienko and D'Agostinoi, NEJM , multiplicity considerations in clinical trials NEJM 2018;378: 2115-22

if a significant treatment effect was achieved in subpopulation 1 then subpopulation 2 needed to achieve a p value of under .05, and if met then the third subpopulation only needed to achieve a p value of 0.05. However if subpopulation one did not achieve a statistically significant result (see figure 3).

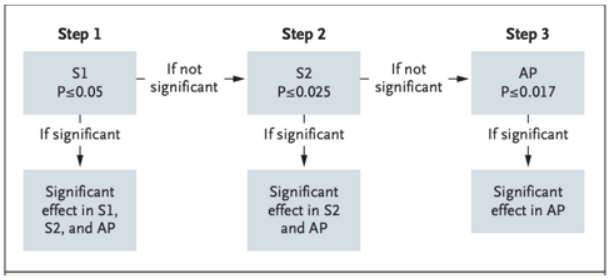
FIGURE 3 -DIFFERENT COHORTS IN APEX TRIAL

Population	P Value (Betrixaban vs. Enoxaparin)	Fixed-Sequence Test	Hochberg Test
Subpopulation 1	0.054	No significant effect	No significant effect
Subpopulation 2	0.03	No significant effect	No significant effect
All-comers population	0.006	No significant effect	Significant effect

Subpopulation one was patients with a D Dimer at least two times over upper limit of normal. Population two is those in subpopulation one who were also over 75 years of age. All comers is all patients who could be evaluated for the primary efficacy outcome. All comers should have been subpopulation one in the fixed sequence test since they are the most important subpopulation .
Adapted from Dmitrienko and D'Agostino, NEJM , multiplicity considerations in clinical trials NEJM 2018;378: 2115-22

then even if the second and third populations achieve p values of less than .05, the entire study was to be viewed only as hypothesis generating. This underscores a limitation of the fixed sequence test in that the use of this test can only be justified if the most significant p value is expected in subpopulation one, which was not the case in APEX. The Hochberg test**,** (see figure 2)

FIGURE 2-HOCHBERG TEST IN THE APEX TRIAL



In the Hochberg test, if one achieves a significant result in subpopulation population 3 in this trial called AP for all comers then even if S1 and S2 are not significant, if subpopulation reaches a low enough p value, the intervention is viewed as significant Adapted from Dmitrienko and D'Agostino, NEJM , multiplicity considerations in clinical trials NEJM 2018;378: 2115-22

on the other hand, tests subpopulation 1 first because it corresponds to the highest p value. Even if subpopulation 1 does not achieve significance, if subpopulation 2 or 3 have low enough p values the study would be successful. Therefore based upon the fixed sequence test the APEX study was viewed as negative but using the Hochberg test it was positive.

Ultimately the FDA felt the Hochberg test was more appropriate because subpopulation 3, which consisted of all patients who could be evaluated for the primary efficacy outcome, was deemed to be more important than subpopulation 1, which consisted of only patients with elevated D Dimer levels. The choice of approach to addressing multiplicity considerations strongly impacted the FDAs decision to approve Betrixaban for post hospital discharge DVT prophylaxis in high-risk medical patients.

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A New Approach to Cancer Screening Guidelines

Lise M. Helsingen, Gordon Guyatt

Given the harms and burdens, how much benefit would most people require to undergo screening for cancer? Even though this question is crucial, until now it has never been addressed explicitly in guidelines for cancer screening. We recently took part in the development of a colorectal cancer screening guideline in which we used a new approach to make explicit judgements about peoples' values and preferences (1).

The guideline panel defined thresholds of benefit below which most people would decline screening, and above which they would likely choose screening. Before examining the benefit, the panel reviewed the harms, burdens and practical issues associated with screening. Considering these undesirable consequences, the panel completed surveys assessing how much benefit typical people would require to undergo screening. Based on the survey results, the panel defined thresholds of required benefit. For example, for screening with faecal immunochemical testing every year for 15 years the panel estimated that a typical threshold to undertake screening would be a reduction in colorectal cancer deaths of 5 per 1000. Bearing these thresholds of required benefit in mind, the panel examined the full body of evidence and issued their recommendations.

Novel recommendations

This is the first guideline of colorectal cancer screening to avoid a blanket recommendation for screening for all above a certain age. The guideline panel found that the pre-defined threshold of required benefit was reached when the cancer risk over 15 years was 3% or higher. Therefore, the panel suggested that for a 15-year risk of colorectal cancer of 3% or higher the majority of fully informed individuals would likely choose screening, but when the risk is lower the majority of individuals are likely to judge that benefits do not outweigh harms and burdens. The panel therefore emphasized shared decision making based on balanced information about absolute benefits, harms and burdens of screening.

Several advantages

Setting a threshold for the required benefit before reviewing the evidence of screening benefit enabled us to make explicit and transparent judgments regarding individual's values and preferences. Our approach also facilitates efficient and coherent recommendation development across a range of individual prognosis. Further, it minimizes the influence of panelists pre-conceived beliefs regarding appropriate recommendations. The approach may be suitable also for other decisions in which one key beneficial outcome is weighted against potential harms and burdens. It works well for cancer screening because disease-specific mortality is the most important expected benefit.

The guideline is a BMJ Rapid Recommendation – a collaborative project between The BMJ and the MAGIC Evidence Ecosystem Foundationthat aims at accelerating new evidence into practice.

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The Big Data Era and Evidence Based Medicine: A Future Vision for a New Challenge.

Ramón Puchades

With the development of bioinformatics and biomedicine, the influence of pure sciences in clinical research is expanding the capacity to treat an amount of data not previously managed. In this sense, Big Data will change (-or is changing) clinical epidemiology[1]. EBM will need an adaptation process in order to deal with this new era, in terms of methodology and data analysis. Big Data may, or may not, increase the precision and accuracy of diagnosis and – less likely – more accurate estimates of treatment effects. Hence, for example, data bases of millions could identify risk difference in the vicinity of 5 to 7% corresponding to NNTs of 15 or 20. On the other hand, Big Data analytics can manage an N of millions for an objective of a risk difference of 100% and a corresponding NNT of 1 if the result is a completely accurate identification of responders. However, although these objectives are ideals, Big Data could represent overinformation and become more a problem than a solution. The challenge for EBM is to develop and implement methods to filter this overinformation, and determine its validity, results and application.

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Is Dietary Saturated Fat Harmful? Epidemiology vs. Evidence Based Medicine

Eric C. Westman

Acknowledgments/Conflicts: Past President: Obesity Medicine Association. Author royalties: Keto Clarity, Cholesterol Clarity. Equity interest: Adapt Your Life, a low-carb education and product company.

In 1998, after two of my patients had success doing the Atkins Diet, and both of their lipid profiles improved— I observed an anomaly. Going against everything I had learned about the dietary fat/heart disease hypothesis, these patients lost weight and their cholesterol levels got better when eating saturated fat. How could this be? My team's curiosity helped to start the scientific evaluation of low-carb, high-fat diets.

At the same time that our early research was going on, several journalists documented the story that the widespread nutritional guidelines to restrict saturated fat were based on epidemiological studies, and the subsequent attempts to show that saturated fat was harmful in randomized, controlled, clinical trials were repeatedly unsuccessful.

From my vantage point, I think that the difference in opinions about dietary saturated fat derives from the tension between "big E" epidemiology and "small e" clinical epidemiology (evidence-based medicine). There is a big difference in the valuation of observational data between the epidemiologists and the clinical epidemiologists. The organizations that bring together "big E" Epidemiologists will emphasize the findings from observational research, including nutritional epidemiology. Epidemiologists have no problem giving guideline recommendations based on observational, non-experimental data—it's all they have. A *clinical* epidemiologist categorizes all of this research as "hypothesis generating"—or a "good idea to then test in a randomized controlled trial", and reports that, according to the GRADE system, observational data for effectiveness begins as low certainty evidence.

During my training, I travelled to McMaster in 1989 for a workshop on "How to Critically Appraise the Medical Literature," and was tutored by Jim Nishikawa. Over the next 10 years I learned about evidence-based medicine at the Society of General Internal Medicine from David Sackett, Brian Haynes, and Alvan Feinstein (Yale). Trained as a clinical epidemiologist, it was easy for me to accept that nutritional epidemiology was "hypothesis generating" and not "hypothesis testing." "Association does not prove causation," a clinical epidemiologist says.

After many clinical trials were published, we opened a university-based obesity medicine clinic in 2006, and have used the low-carb ketogenic diet as the default treatment for patients with a wide variety of medical conditions.(Westman, Nordmann, Bueno) I personally have treated about 5,000 patients and have seen no clinically apparent harm in advising patients to eat saturated fat. To the contrary, I observe improvements in obesity, diabetes,

hypertension and a host of other medical problems and complaints. In 2010, a meta-analysis of observational studies was published showing that consumption of saturated fat was not associated with cardiovascular disease.(Siri-Tarino) McMaster has now entered the nutritional epidemiology world with the PURE study, an observational study that followed 135,000 participants from five continents, and found that saturated and unsaturated fats were not significantly associated with risk of myocardial infarction or cardiovascular disease mortality.(Dehgan)

If you still believe that there is good evidence to restrict dietary saturated fat, then I recommend that you start with the books by the journalists Gary Taubes and Nina Teicholz. Yes, it IS possible that both positions are correct: that saturated fat IS bad when carbohydrates are consumed, AND saturated fat is NOT bad when carbohydrates are *not* consumed. In other words, the low-carb diet is simply a situation when eating saturated fat is not harmful—because you are burning it for fuel. However, I have serious doubts about saturated fat being bad even in the context of a high carbohydrate intake because these pioneering books helped me to understand the weak observational studies upon which the restriction of saturated fat was founded in the first place. Based on my research and clinical experience, I believe that there are many healthy eating patterns, and that keeping glucose and insulin low is the healthy common denominator whether someone is eating saturated fat or not.(Reaven, Volek)

So, I feel comfortable in advising people it is okay to eat saturated fat and limit carbohydrates because evidence-based medicine supports eating many healthy eating patterns, including low carb, high fat diets.

Recommended reading:

The story of the low-fat diet

1. Taubes, G. Good Calories, Bad Calories. Fats, Carbs, and the Controversial Science of Diet and Health. Anchor Books, 2007.
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Observational studies showing no relationship of dietary saturated fat and disease

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Metabolic syndrome, insulin resistance, and cardiometabolic risk

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Other resources

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3. Ketogenic Diet and Metabolic Therapies. Expanded Roles in Health and Disease. Masino SA, Ed. Oxford University Press, 2017.

User Involvement in the Recommendation Development Process to Improve Guideline Adherence

Ariel Izcovich, Martin Ragusa,
Marzio A Lavena, et al.

Background: one of the most attractive alternatives to narrow the evidence-practice gap is the implementation of trustworthy clinical practice guidelines. Although the last decade has seen significant advances in guideline 9methodology, important limitations still remain. Furthermore, healthcare workers frequently consider that guideline recommendations are alien to their context. This situation reduces recommendation adherence. We hypothesized that including potential guideline users in the recommendation's development process would increase compliance.
Objectives: to evaluate if a strategy that incorporates clinicians (recommendation users) in the process of recommendations development is feasible and improves recommendation adherence.
Methods (figure 1): the study was carried out in the internal medicine department of the German hospital in Buenos Aires, Argentina, between March and December 2018. Study participants (clinicians working in the department) identified 40 relevant clinical questions that were included in our study and randomized to intervention and control arms. We developed recommendations in response to the 20 questions assigned to the intervention arm following the GRADE approach. In 45-minutes meetings, the study participants, constructed recommendations in response to those questions using Evidence to Decision frameworks and summary of findings tables developed by two GRADE methodologists. To answer the questions assigned to the control group, we adopted published recommendations. All the recommendations (intervention and control) were included in an easily accessible webpage and considered as official guidance. We prospectively identified recommendation adherence opportunities (situations in which an opportunity to adhere to one of the 40 recommendations existed) and recorded whether the clinician's course of action was consistent with the direction of the proposed recommendation (recommendation adherence). We calculated the relative risk and 95% confidence interval (CI) of recommendation adherence between intervention and control arms. In order to adjust for potential confounding, we constructed a logistic regression model considering several variables. Additionally, to account for the clustered nature of the data we performed a sensitivity analysis considering study questions as the units of analysis.

Results: during the study period, we identified 1004 recommendation adherence opportunities corresponding to the questions assigned to intervention and 1987 to control. Adherence to recommendations in response to questions assigned to the intervention arm was higher than those assigned to the control group, adjusted estimate, odds ratio (OR) 2.14 (95% CI 1.6 0to 2.83). Sensitivity analysis accounting for the clustered nature of the data informed a non-statistical difference between the study arms, P = 0.27.

Conclusions: including guideline users in the recommendation development process was feasible and may increase recommendation adherence.

Figure 1. Methods

SOURCE Evidence-Based Surgery Program Update

Achilles Thoma, Jessica Murphy

For many reasons, the past year marked a significant time for the Surgical OUtcomes Research CEntre (SOURCE). In February 2019 four of the SOURCE tutors ran the 19th annual evidence-based surgery workshop. This year, the attendees (surgeons, surgical fellows, surgical residents and research assistants) learned how to appraise surgical articles focused on Health-Related Quality of Life. As in the past, the attendees provided useful feedback, reporting that the workshop met all their expectations and improved their critical analysis skills.

In March 2019, the book, "**Evidence-Based Surgery: A Guide to Understanding and Interpreting the Surgical Literature**" was released by Springer Publishing. The editors of the book: A.Thoma, S.Sprague, S. Voineskos , C.Goldsmith are all SOURCE members.

This book is geared to surgeons of all specialities and settings (i.e.: academic or community). The objective is to teach these individuals how to critically appraise the results of published surgical clinical research before applying findings to their practice. With 380 pages and over 30 chapters, readers learn how to appraise information based on specific areas within the surgical literature. Examples of the chapters include: (1) randomized controlled trials in surgery, (2) surgical case series, (3) systematic reviews, (4) economic evaluations of surgical interventions, and (5) clinical practice guidelines. Each chapter begins with a surgical clinical scenario, followed by an introduction to the theme of the chapter, a literature search to find the best evidence, and a set of questions to appraise an identified article. So far, feedback from the book has been extremely positive. The book is available online from Amazon or the Springer Book Store.

Following this milestone, one of the editors (A.Thoma) who has served as the Director of SOURCE for over 10 years announced that the 2018-2019 year would be his last term. During his term as Director, SOURCE held several local and international workshops, continued with the publications in the "Users' Guides to the Surgical Literature" article series, published in the Canadian Journal of Surgery, and published the above-mentioned book, inspired by this series.

The role of SOURCE within McMaster will continue under the direction of a new Director, to be announced at a later time. Please stay tuned for more information on future workshops.

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PythonMeta: A Python Package for Meta-Analysis

Deng Hongyong

As a versatile and robust programming language, Python is favoured by computer users for its concise code, powerful functions, and flexible deployment. It has unique advantages in data collection, analysis, and visualization. The power of Python depends on third-party modules, and although there are many excellent computing and statistics modules (such as Pandas, statmodels, etc.), they are not yet sufficient for complex, customized meta-analysis. Therefore, we have developed a Python meta-analysis package, PythonMeta, to devise meta-analysis algorithms and statistical tests for different data types, and to generate graphical results.

PythonMeta programs under the Python3.x (e.g., 3.6) framework import the data pre-processing and scientific computing of NumPy and develop visualizations based on the Matplotlib graphics library. The current version of the PythonMeta package contains three main classes, i.e., Data, Meta, and Fig, and more than 10 callable functions. It can be used for heterogeneity testing of dichotomous data and continuous data, effect-size (relative risk, odds ratio, risk difference, mean difference, and standardized mean difference) combinations with algorithms (Mantel-Haenszel, Peto, Inverse Variance, DerSimonian and Laird, etc.) of fixed and random effect models, and additional functions, such as subgroup analysis, cumulative meta-analysis, and sensitivity analysis. All analysis results can be customized to text, tables, or graphs (Forest plots and Funnel plots). PythonMeta implements third-party support for meta-analysis in Python, which is suitable for the development of desktop, server, Web, embedded API, and other application scenarios. Compared with the existing meta-analysis software, PythonMeta has the following advantages:

1. Cross-platform interoperability (Python and its modules are supported in Windows, iOS, and Linux);
2. Functions can be highly customized according to various needs;
3. Network support, i.e., an online meta-analysis service can be easily realized.

The latest PythonMeta package is distributed on the Python developer community (PyPI, https://pypi.org/project/PythonMeta/) for free installation. An online meta-analysis tool (http://www.pymeta.com) based on the PythonMeta module has also been successfully launched to provide free services for users.

GRADE Provides Guidance about how to Communicate the Results of Systematic Reviews

Nancy Santesso

Challenges communicating results

If you ever had to read or write the conclusions of a systematic review, or summarise the results of a systematic review for health care professionals, patients, or other decision makers, then you know that it can be difficult. Imagine that you found moderate certainty evidence that the risk ratio for the effect of vitamin D compared to placebo on preventing hip fractures is 0.89 (95% CI, 0.63 to 1.18), how would you express this effect simply to readers? We have seen some creative ways to convey results: 'the evidence shows that there is at best, a modest, non-statistically significant trend in favour of vitamin D'; 'there is evidence of no effect'; or 'there is no evidence of effect'. Unfortunately, statements like these are suboptimal.

Two important concepts: size of effect and certainty of evidence

To help authors write informative statements about their results, GRADE has developed guidance. The approach for communicating results is built around two concepts: 1) the size of the effect; and 2) the certainty we have in the effect. The size of the effect is typically informed by absolute effects on an outcome (e.g., 5 fewer people out of 100 will have a hip fracture). The certainty is informed by an assessment of the evidence for an outcome: high, moderate, low, or very low.

The guidance

Consider the example above about vitamin D where there is moderate certainty evidence that the risk ratio for the effect of vitamin D compared to placebo on hip fractures is 0.89 (95% CI, 0.63 to 1.18). We can use the Table below to write the statement following these steps:

1. select the category for certainty of evidence – in this case it is moderate due to imprecision
2. make a judgement about the size of the effect using absolute effects. We can convert the relative effect to absolute using a baseline risk of hip fracture as 20 per 1000 people, and calculate the difference in effect as 2 fewer people per 1000 have a hip fracture. The size can be categorized as large, moderate, small but important, or trivial/little to no effect. In this case, we can judge it to be a small but important effect, and will see options for statements using the word 'slightly'
3. choose one statement from the appropriate wording options. For a small important effect of moderate certainty, the statement is "vitamin D likely reduces hip fractures slightly"

Alternatively, if you use software, such as GRADEpro (http://www.gradepro.org), you will automatically be provided with options based on the effect and the certainty of evidence. It will still be up to you to decide whether the size of the effect is large, moderate, small but important, or trivial/little to no effect.

Use of the statements

Authors of systematic reviews can communicate results using simple statements in the abstract, a plain language summary, results, discussion, and in evidence tables. Authors can also use the statements in tools and products that communicate the results of systematic reviews to decision makers, such as in the section of health care guidelines where the evidence is summarized.

The statements were originally developed to communicate the results of systematic reviews of interventions, but can be used in reviews of test accuracy (diagnosis) or prognosis. For example, the word 'associated' could be used in a review of risk factors for hip fractures, where the statement for a moderately sized association of hip fractures with

age based on low certainty evidence could be written as 'age may be associated with hip fractures'.

The research to develop the statements and the future

We first developed the statements over 10 years ago and evaluated them in patients and consumers through user testing, qualitative analysis and a randomised controlled trial.[1,2] The system back then provided writers with one statement to communicate evidence per each of the four levels of certainty of evidence and three sizes of effect. Informal feedback indicated that people would like to have more options for the statements. After a series of workshops and meetings to obtain more formal feedback, we surveyed writers and readers of systematic reviews and guidelines about the acceptability of additional statements. Some options were deleted, such as 'it *appears* that the intervention increases outcome', because 'appears' sounded too supernatural. Based on the results, other options were finalised and the system was approved by the GRADE Working Group.

The statements were developed with user testing in multiple languages. In addition, the approach could be applied to other types of systematic reviews and the acceptability of other statements tested.

For more information about this guidance, see the following article in press: https://www.jclinepi.com/article/S0895-4356(19)30416-0/fulltext

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Table: Final list of statements to communicate results of systematic reviews

Size of the effect estimate	Suggested statements *(replace X with intervention, replace 'reduce/increase' with direction of effect, replace 'outcome' with name of outcome, include 'when compared with Y' when needed)*
HIGH Certainty of the evidence	
Large effect	X results in a large reduction/increase in outcome
Moderate effect	X reduces/increases outcome X results in a reduction/increase in outcome
Small important effect	X reduces/increases outcome slightly X results in a slight reduction/increase in outcome
Trivial, small unimportant effect or no effect	X results in little to no difference in outcome X does not reduce/increase outcome
MODERATE Certainty of the evidence	
Large effect	X likely results in a large reduction/increase in outcome X probably results in a large reduction/increase in outcome
Moderate effect	X likely reduces/increases outcome X probably reduces/increases outcome X likely results in a reduction/increase in outcome X probably results in a reduction/increase in outcome
Small important effect	X probably reduces/increases outcome slightly X likely reduces/increases outcome slightly X probably results in a slight reduction/increase in outcome X likely results in a slight reduction/increase in outcome
Trivial, small unimportant effect or no effect	X likely results in little to no difference in outcome X probably results in little to no difference in outcome X likely does not reduce/increase outcome X probably does not reduce/increase outcome
LOW Certainty of the evidence	
Large effect	X may result in a large reduction/increase in outcome The evidence suggests X results in a large reduction/increase in outcome
Moderate effect	X may reduce/increase outcome The evidence suggests X reduces/increases outcome X may result in a reduction/increase in outcome The evidence suggests X results in a reduction/increase in outcome
Small important effect	X may reduce/increase outcome slightly The evidence suggests X reduces/increases outcome slightly X may result in a slight reduction/increase in outcome The evidence suggests X results in a slight reduction/increase in outcome
Trivial, small unimportant effect or no effect	X may result in little to no difference in outcome The evidence suggests that X results in little to no difference in outcome X may not reduce/increase outcome The evidence suggests that X does not reduce/increase outcome
VERY LOW Certainty of the evidence	
Any effect	The evidence is very uncertain about the effect of X on outcome X may reduce/increase/have little to no effect on outcome but the evidence is very uncertain

Machine Learning In Evidence Synthesis

Nigar Sekercioglu

Machine learning algorithms and statistical learning methods are employed to develop and validate predictive or classification models in clinical medicine. Traditional methods include discriminant analysis, Poisson regression, generalized estimating equations, and generalized additive models whereas machine learning algorithms include tree-based methods (e.g. single classification trees and random forests), artificial neural networks, support vector machines, and Bayesian belief systems[1]. Machine learning methods (supervised learning with known outcomes and unsupervised learning without known outcomes) learn from the data while accommodating complex relationships between variables when interactions and non-linear relationships exist or are suspected[1].

These models also handle numerous predictors with potential influences on clinical outcomes and are very flexible. Therefore, regularization methods are needed to create penalized coefficients and handle overfitting. Statistical learning methods, on the other hand, are based on theory and assumptions and lack the capacity to address and explain complex relationships between predictors and outcomes. The main purpose of using these algorithms is to synthesize and interpret the data.

Additionally, machine learning algorithms have been used in topic analysis to identify relevant studies in the context of evidence synthesis. Mo *et al*. employed unsupervised machine learning techniques using the support vector machine approach to identify relevant studies for their systematic review[2]. Their results showed the method might reduce the workload in the title and abstract screening phase. Machine learning may hold promise for screening of large amounts of data, whether text or numerical, and for pattern recognition.

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From Medical Librarian to EBM Clinical Research Documentarist

Cecilia Pacheco V.

The first printed medical database was Index Medicus, developed by the USA National Library of Medicine, published in 1879 with 20,169 articles. With the growth of research, the number of indexed citations has increased exponentially. The challenge for healthcare providers is how to get a quick answer to their clinical questions.

With the emergence of evidence-based medicine, the need to efficiently find scientific support for clinical decisions has increased. Physicians can find critical support for this task by partnering with medical librarians, who can assume the role of clinical research documentarists. This partnership can help transform a clinical question into a PICOT format question (population, intervention, control outcome and time frame), which can then be used to search electronic literature databases (e.g. PubMed) for relevant citations.

Evidence alone is not sufficient to inform clinical decision-making, and both the clinical knowledge of healthcare providers and patient's values and preferences require consideration. However, partnering with medical librarians to efficiently locate the highest quality research to inform clinical questions is an important starting point.

My Experience With the Evidence Based Clinical Practice Workshop (EBCP Workshop)

Rodrigo Gil

Many years ago, I started a Journal Club for fellows, internal medicine residents and staff physicians that has been well received, but I do not have a formal training in Evidence Based Medicine other than

some courses, including the ATS Methods in Epidemiologic, Clinical and Operations Research (MECOR). In April 2019 I attended the EBCP Workshop in McMaster because I wanted to learn new approaches to teach Evidence Based Medicine, and I had a great experience.

The EBCP Workshop, including the pre course, allowed me to review basic and advanced Evidence Based Medicine concepts in large group presentations and small group tutorials.

My experience in the small groups was terrific, not only for the knowledge of the tutors and the librarian but also for the process of interaction and feedback among us: direct, clear, respectful and with a good sense of humor. During the workshop we were asked to highlight both the positive and negative aspects of presentations, without saying "this is wrong", instead, "this could change", or "you could avoid".

I returned to Chile very excited and decided that in each Journal Club there would be a presentation on some methodological aspect related to the paper under discussion.

For example, when we analyzed the study "Acute Myocardial Infarction after Laboratory-Confirmed Influenza Infection. N Engl J Med 2018; 378: 345-53", we discussed association and causality. On another occasion when we analyzed the paper "Inhaled Tranexamic Acid for Hemoptysis Treatment: A Randomized Controlled Trial. Chest 2018 Dec; 154 (6): 1379-1384," we discussed measures of treatment effectiveness (e.g. RR, RRR, NNT) and also randomized trials stopped early for benefit. We have also dedicated sessions to topics such as hypothesis testing, p-values and confidence intervals.

This new approach has been very well received, and the Fellows have told me confronting unfamiliar methodology and then discussing it, has allowed them a better understanding of the study results. The Users´ Guides to the Medical literature has been very useful for preparing these presentations, and as a resource for the Journal Club tutors. We are planning to write up our experiences and publish it in a format similar to the ACP Journal Club in the "Revista Chilena de Enfermedades Respiratorias", the journal of our Society.

I highly recommend doing this course to anyone who wants to learn EBM or learn to teach EBM.

McMaster Evidence-Based Clinical Practice Workshops

Experience the BEST in EVIDENCE-BASED Health Care Education

Monday, June 8th - Friday, June 12th, 2020

Come to McMaster, the birthplace of evidence-based health-care, where we offer an optional pre-course in addition to one of two closely related workshops. The first caters to clinicians who wish to improve their clinical practice through enhanced skills in reading, interpreting, and applying the medical literature. The second is designed for clinician educators interested in enhancing their skills for teaching the principles of evidence-based practice to others. Both workshops are tailored to faculty and community internists, hospitalists, and senior and incoming chief residents. Our website: https://ebcp.mcmaster.ca

What is Evidence-Based Clinical Practice/Evidence-Based Medicine?

Evidence-based clinical practice (EBCP) is an approach to health-care practice that explicitly acknowledges the evidence that bears on each patient management decision, the strength of that evidence, the benefits and risk of alternative management strategies, and the role of patients' values and preferences in trading off those benefits and risks.

Why are Evidence and Values or Preferences Important?

Clinicians are confronted daily with questions about the interpretation of diagnostic tests, the harm associated with exposure to an agent, the prognosis of a disease in a specific patient, the effectiveness of a preventive or therapeutic intervention, and the relative costs and benefits associated with these decisions. Both clinicians and policy makers need to know whether the conclusions of a primary study or a systematic review are valid, and whether recommendations in clinical practice guidelines are sound.

Members of the Health Research Methods, Evidence, and Impact (HEI) at McMaster University, in collaboration with other colleagues trained in both medicine and in clinical epidemiology, have developed a set of common sense strategies to assist in the critical appraisal of evidence. They have also developed approaches explicitly considering values and preferences in clinical decision-making, thereby encouraging the practice of EBCP.

Workshop Objectives

Optional Pre-course: An additional 4-hour large group setting pre-course for individuals wishing for an overview or refresher on **"Basic EBM Concepts"**. The pre-course requires separate registration and fees in addition to the main workshop registration. Participants must register for the Workshop to be eligible to take the Pre-course. This Pre-Course will start in the morning on Monday, June 8, 2020. See our website for more information (click "What to Expect" and then "Pre-Course").

Optional Post-course: An additional 3-hour large group setting post-course for individuals wishing to understand **"Developing an EBHC Curriculum"**. The post-course requires separate registration and fees in addition to the main workshop registration. Participants must register for the Workshop to be eligible to take the Post-course. This Post-Course will start in the afternoon on Friday, June 12, 2020. See our website for more information (click "What to Expect" and then "Post-Course").

Both streams: To help participants advance their skills in critically appraising the literature, and their skills in acknowledging and incorporating values and preferences in clinical decision-making.

Improve your practice stream: To acquire an understanding of common epidemiological concepts (e.g. interpreting hazard ratios, confidence intervals, critical appraisals of a systematic review) and advance their skills in using the literature for quality assurance, improving practice, and judging comparative effectiveness of health care interventions.

Teaching stream: To help participants learn how to teach EBCP using a variety of educational models in different settings, with different types of learners.

Workshop Format

The workshop is offered as a one-week intensive course in small group format. Participants will be learning in interactive small groups led by clinical epidemiologists and practitioners from McMaster and other institutions. The workshop will consist of small and large group sessions, individual study time and, *for the teaching stream, opportunities for workshop participants to lead teaching sessions using their own ideas, materials, and reflecting their own experiences*.

What to Expect EBCP Workshop Improve Practice Stream Specifics - <u>Learning Objectives:</u>

To help participants advance their skills in critically appraising the literature and their skills in acknowledging and incorporating values and preferences in clinical decision making. To acquire an understanding of common epidemiological concepts (e.g. interpreting hazard ratios, confidence intervals, critical appraisals of a systematic review) and advance their skills in using the literature for quality assurance, improving practice, and judging comparative efectivness of health care interventions.

Who Should Attend<u>:</u>

Clinicians, physicians, nurses, pharmacists, occupational and physiotherapists, dentists, chiropractors and other health-care professionals with limited prior exposure to concepts in evidence-based practice.

Improve Practice Stream Format:

The workshop uses small-group formats for participants to acquire new EBP skills, and to practice those skills. Learners will be expected to actively engage in small group learning including identifying learning priorities and sharing responsibility for the learning environment in the small group. For example, learners will be asked to identify key papers, concepts and examples of evidence that matters to their home practice. Learners will actively problem solve, critically appraise articles and verbalize key EBM concepts to facilitate understanding.

What to Expect EBCP Workshop Teach Stream Specifics <u>- Learning Objectives:</u>

To help participants advance their skills in critically appraising the literature, and their skills in incorporating values and preferences in clinical decision making.

To help participants advance their skills in ***teaching EBCP*** using a variety of educational models in different settings, with different types of learners.

Who Should Attend:

Physicians, nurses, pharmacists, occupational and physiotherapists, dentists, chiropractors and other health-care professionals who have an understanding of the fundamentals of EBCP who anticipate future opportunities to teach the skills of EBCP to their learners.

Teaching Stream Format:
What many people don't realize: If you enroll in the teaching stream, ***you will be doing some of the teaching***. The workshop uses small-group formats for participants to acquire new EBP teaching skills and to practice those skills. Role play will simulate the teachig environments of the participants.

Workshop Materials
Prior to and at the workshop, participants will have access on-line to educational materials that include literature on critical appraisal and EBCP, the small group learning format, a set of clinical problems, JAMA evidence, and a variety of other EBCP aids.

Why Come to McMaster University?
McMaster University is not only the birthplace of evidence-based medicine, and has produced the definitive evidence-based health care texts, we also continue to lead the world in innovation and advances in EBHC practice and teaching. McMaster's workshop, running for more than 25+ years, has provided the model for EBHC workshops throughout the world. Over this time, we have developed a cadre of the best EBHC educators in North America who return to the workshop year after year because of the intensely stimulating and educational environment. Come to experience the best in EBHC education!

Travel Facilities and Accommodation
The workshop will be held at McMaster University. Upon confirmation of a definite placement in the workshop, you will receive a formal letter, access to the website and background and introductory materials will be provided with general information regarding specifics of the workshop, accommodation and travel.

Travel and accommodation arrangements are the responsibility of the Registrant. Modest accommodation is available on campus. Other accommodations are available in city hotels, 10-30 minutes away by foot, bus or car.

Registration Fees

$200 discount if you register before Dec 31, 2019

REGISTRATION FEES	Canadian $	
Optional Pre-course *– Basic EBM Concepts*	$ 400.00	+ 13% Harmonized Sales Tax
Optional Post-course *– Developing an EBHC Curriculum*	$ 300.00	+ 13% Harmonized Sales Tax
One member from an institution	$2800.00	+ 13% Harmonized Sales Tax
Two members from an institution	$2500.00 each	+ 13% Harmonized Sales Tax
Three or more members from an institution	$2200.00 each	+ 13% Harmonized Sales Tax

13% Harmonized Sales Tax (HST # R119-035-988).
Registration fee includes, 3rd Edition – Users' Guide to the Medical Literature, photocopying services, access to computer literature searching, Lunch for Pre-Course Participants and dinner on the first and last evenings.

Register online at: https://ebcp.mcmaster.ca/

You will receive an invoice with instructions after your ONLINE registration.

Please refer to your registration number in all correspondence.

NOTE: (CANADIAN & US) PAYMENT *BY CHEQUE ONLY*.
(INTERNATIONAL) PAYMENT *BY WIRE TRANSFER*

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If you would like to encourage a colleague to attend the workshop next year, please e-mail graing@mcmaster.ca or write the address here and send to Laurel Grainger, HEI, HSC 2C12, McMaster University Health Sciences Centre, 1280 Main Street West, Hamilton, ON L8S 4K1, Canada. Thank you!

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