PRISMA Statement

To the Editor:
In their recent commentary Takkouche and Norman seriously misrepresent the PRISMA guideline for reporting systematic reviews and meta-analyses. They state that PRISMA “demand[s] the prior registration of the protocol of any systematic review and meta-analysis, requiring that this protocol should be made accessible before any hands-on work is done.” No such demands are made in PRISMA. Item 5 of the checklist asks authors to “Indicate if a review protocol exists, if and where it can be accessed (such as Web address), and, if available, provide registration information including registration number.” The rationale for this request is: “registration may reduce unnecessary duplication of the same review question, particularly in jurisdictions with limited budgets; minimize study publication bias and selective reporting bias; and provide important information for those involved in updating systematic reviews.” That request anticipated the development of SR registration; indeed an international register is now being developed.

Likewise, the PRISMA reporting guideline makes no statements as to the need for publication of a protocol prior to the initiation of the systematic review. It is possible that, as with the advent of clinical-trial registration, more avenues will appear whereby authors can publish protocols of such reviews. The authors also misrepresent the nature of registration, suggesting that this process would involve a judgement of originality and scientific merit of the planned research; we know of no such proposal.

Takkouche and Norman also state “We also dispute the view that sub-group analyses and similar approaches should be used only if they were prespecifid.” Again PRISMA makes no such demands on authors. Rather, the PRISMA explanatory paper says: “Having a protocol can help restrict the likelihood of biased post hoc decisions in review methods, such as selective outcome reporting.”

In our explanatory article about PRISMA, we also recognized that “Authors may modify protocols during the research, and readers should not automatically consider such modifications inappropriate.” PRISMA seeks transparency and clarity: authors need to report how the systematic review was conducted to enable all readers to decide upon its merits.

Lastly, we are not as confident as Takkouche and Norman about the effectiveness of peer review. A recent systematic review indicates that the peer review process is at best marginal and at worst ineffective. The scant research into the decision-making process of editors supports the need for clear and transparent reporting.

The authors respond:
We thank the authors for their interesting comments in defense of their proposed guidelines. However, we judge their remarks to be about semantics, not substance. The authors themselves have previously stated that PRISMA advocates protocol registration. In our view, the main issue is not whether PRISMA “demands,” “advocates,” or “requests” registration. If the guideline was adopted as standard by journal editors, the “request” would of course become a requirement, and the real question is whether this requirement makes sense. Our view, as detailed in our original commentary, is that it does not: this additional layer of academic bureaucracy would merely obstruct free scientific enquiry.

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Nonalcoholic Fatty Liver Disease and Acute Ischemic Stroke

To the Editor:

Nonalcoholic fatty liver disease is associated with a higher risk of self-reported cardiovascular disease.1 A recent systematic review also found persons with nonalcoholic fatty liver disease to have a 13% relative increase in carotid intima-media thickness.2 The risk of acute ischemic stroke in relation to inflammatory markers of nonalcoholic fatty liver disease remains unknown.

We conducted a cross-sectional records-based study at the London Health Sciences Centre in London, Ontario. We included adults aged 20 to 75 years with suspected acute stroke between January 2005 and December 2009; had undergone diffusion-weighted magnetic resonance imaging (MRI), which is sensitive and specific for early changes of acute ischemic stroke. Persons with an acute ischemic stroke were considered cases, and those whose scan was negative served as controls. Study entry required that a patient have had serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) concentrations measured within 90 days before, or within 72 hours after, the MRI. Patients with evidence of intracranial hemorrhage or malignancy on MRI were excluded.

The primary study outcome was biochemical evidence of inflammatory nonalcoholic fatty liver disease, defined as an elevated serum alanine aminotransferase concentration ≥95th percentile among the controls.

The study was done in accordance with a research protocol approved through the Research Ethics Boards of the London Health Sciences Centre.

We included 103 cases with, and 200 controls without, acute stroke, confirmed by diffusion-weighted imaging MRI. Details of participant characteristics are listed in the eAppendix (http://links.lww.com/EDE/A443).

Transaminases were measured within a median of 2 days (cases) and 17 days (controls) of the diffusion-weighted imaging MRI. The adjusted odds ratio (OR) for acute stroke in the presence of an elevated alanine aminotransferase was 3.3 (95% confidence interval [CI] = 1.3–8.4) (Table). Similar elevations were observed for aspartate aminotransferase concentration, as well as for alanine aminotransferase or aspartate aminotransferase in conjunction with an aspartate aminotransferase:alanine aminotransferase ratio under 2.0 (Table).

A study strength was the inclusion of both cases and controls who underwent sensitive diffusion-weighted MRI imaging for the assessment of acute stroke. This likely reduced the presence of diagnostic suspicion or referral bias,3 and correctly assigned persons with acute stroke as cases and those without acute stroke as controls. Second, we adjusted for a number of stroke risk factors, but not serum triglycerides or hepatic fat on imaging studies.1,4 Others have observed nonalcoholic fatty liver disease to predict the future risk of cardiovascular disease independent of metabolic syndrome.1,4 Among 1221 healthy Japanese men and women, the adjusted OR was 4.1 (95% CI = 1.6–11), but there were only 22 cardiovascular events, of which 12 were self-reported ischemic strokes.5 In a second study of 248 diabetic cases with cardiovascular disease, including just 29 nonfatal ischemic strokes, the associated OR between non-alcoholic fatty liver disease and cardiovascular disease was 1.5 (95% CI = 1.1–1.7).1 Our study, which focused exclusively on acute ischemic stroke, complements these findings.

Confirmatory data are needed regarding whether nonalcoholic fatty liver disease is an independent risk factor for ischemic stroke. If so, then measurement of alanine aminotransferase or aspartate aminotransferase—both of which are readily available and inexpensive—could be considered along with traditional stroke risk factors such as serum glucose, lipids, and blood pressure.

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TABLE. Risk of Stroke Associated With Biochemical Markers of Inflammatory Nonalcoholic Fatty Liver Disease

<table>
<thead>
<tr>
<th>Criterion for Biochemical Presence of Inflammatory Nonalcoholic Fatty Liver Disease</th>
<th>Cases</th>
<th>Controls</th>
<th>Crude</th>
<th>Adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated alanine aminotransferaseb</td>
<td>Absentc 84 (82) 188 (94) 1.0 1.0</td>
<td>Present 19 (19) 12 (6) 3.5 (1.7–7.6) 3.3 (1.3–8.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated aspartate aminotransferaseb</td>
<td>Absentc 90 (87) 190 (95) 1.0 1.0</td>
<td>Present 13 (13) 10 (5) 2.7 (1.2–6.5) 3.6 (1.1–11.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated aspartate aminotransferase:alanine aminotransferase ratio &lt;2.0</td>
<td>Absentc 79 (77) 183 (92) 1.0 1.0</td>
<td>Present 24 (23) 17 (9) 3.3 (1.7–6.4) 3.1 (1.4–7.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for age (continuous in years), sex, current smoking, current heavy ethanol intake, history of hypertension, or current use of an antihypertensive agent, atrial fibrillation, LDL-cholesterol concentration (continuous in mmol/L), serum glucose concentration (continuous in mmol/L), and serum creatinine concentration (continuous in µmol/L).

bAn alanine aminotransferase (40.0 U/L) or aspartate aminotransferase (37.5 U/L) concentration.

cReference category.

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Risk of Parotid Malignant Tumors in Israel (1970–2006)

To the Editors:

Major salivary gland cancers are rare and with few known risk factors. We have analyzed the incidence and epidemiologic features of major salivary gland cancer (ICD.C07–C09) using data from the Israel National Cancer Registry, 1970–2006.

The annual incidence of major salivary gland cancer was 0.8 cases per 100,000. The most common subtype of salivary gland tumor was salivary gland carcinoma (60% of all cases) followed by squamous cell carcinoma (18%) and lymphoma (10%). Of 1924 cases (1039 men, 885 women), 60% were in the parotid gland, 7% in the submandibular gland, and fewer than 1% in the sublingual gland; the remaining 33% were recorded as overlapping or not otherwise specified (ICD.C08.8, 08.9).1 Our results for sex, age, site, tumor type, and rate per year are similar to those reported in the literature. Comparing the parotid gland tumors with all other salivary gland locations, there were no important differences in risk by sex, age, or ethnicity.

Trends for parotid gland cancers have seldom been reported, and have not been compared with other types of salivary gland tumors. The total number of parotid gland cancers in Israel increased 4-fold from 1970 to 2006 (from 16 to 64 cases per year), whereas other major salivary gland cancers remained stable (Fig. 1). The steepest increase occurred after 2001, with an average of 37 cases of parotid gland cancer annually before that date and 61 cases per year subsequently. The distribution of cases by age, sex, or tumor type did not change substantially during this time. The population of Israel increased 2.1-fold from 1970 to 2001, but only 1.1-fold from 2001 to 2006.2 Population growth could not, therefore, explain the increased number of parotid gland cancers.

The proportion of major salivary gland cancers “not otherwise specified” declined from 36% before 2001 to 13% during 2001–2006. This shift may have contributed to changes over time in specific diagnoses. Nevertheless, even if we assume that all cases not-specified were parotid gland cancers, there remains a substantial increase of parotid gland cancers with time (72 cases per year after 2001 compared with 44 cases per year before).

Published data have suggested possible etiologies for major salivary gland cancers, including exposure to radiation (therapeutic and diagnostic), aging, and other factors.3–5 The marked increase of parotid gland cancers in the last decade may reflect differences in an external risk factor specific to the parotid region. The INTERPHONE study6 has investigated parotid gland tumors and other tumors that originate in tissues most exposed and proximal to cellular phones. Israelis are heavy users of cellular phones, with a 6-fold increase in usage (by minutes) from 1997 to 2006.7,8 Investigators have previously suggested a potential association of

FIGURE. For trend analyses, we added regression lines and calculated $R^2$ values. Parotid gland cancer: $R^2 = 0.83$; Submandibular gland cancer: $R^2 = 0.36$; Sublingual gland cancer: $R^2 = 0.02$.  

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parotid gland tumors with cell phones in an Israeli case-control study.\(^7\)

Data on individual exposures to cell phones are not available in the registry data, and no causal association with parotid malignant tumors can be ascertained from these ecologic data. Further research is required to investigate the spectrum of possible etiological factors.

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**On the Link Between Sufficient-cause Model and Potential-outcome Model**

To the Editors:

The sufficient-cause model and the potential-outcome model have now become cornerstones for causal thinking in epidemiology. The link between these 2 models has been discussed.\(^1–3\) We present details of one specific situation to elucidate these 2 different causal approaches. We demonstrate a link between these 2 models under 2 binary causes \(X_1\) and \(X_2\) and a binary outcome \(D\).

We let \(D_{1\omega}(\omega)\) denote the potential outcomes for individual \(\omega\) if, possibly contrary to fact, there had been interventions to set \(X_1 = x_1\) and \(X_2 = x_2\). For each individual \(\omega\), there would thus be 4 possible potential outcomes \(D_{11}(\omega), D_{10}(\omega), D_{01}(\omega),\) and \(D_{00}(\omega)\), which results in 16 (\(= 2^4\)) possible response types.\(^1,4\)

We could enumerate 9 different types of sufficient causes for \(D\) along with certain background causes \(A^k\): \(A_1, A_2X_1, A_2X_2, A_2X_1X_2, A_2X_1X_2, A_2X_1X_2, A_2X_1X_2, A_2X_1X_2, A_2X_1X_2\), where we let \(X\) denote the complement of \(X\).\(^1\) Here, the symbol \(A_\bar{k}\) denotes a set of all components or factors other than the presence of \(X_1, X_2,\) and \(X_\bar{2}\), that may be required for a particular mechanism to operate. An individual is at risk for sufficient cause \(k\) if \(A_k\) is present. We can thus enumerate 512 (= \(2^9\)) possible risk-status patterns for the sufficient causes.\(^2\)

We show in the eTable (http://links.lww.com/EDC/A440) a complete enumeration of the 16 response types and the 512 risk-status patterns for the sufficient causes. Although a particular risk-status pattern in individual \(\omega\) suffices to fix a response type, the converse is not true.\(^2,4,5\) Indeed, potential outcomes are quantities specific to individuals, whereas the sufficient-cause model refers to mechanisms. Nonetheless, response types 7, 8, 10, 12, 14, 15, and 16 correspond to a unique risk-status pattern.\(^5\)

In some cases, the effects of \(X_1\) may be in the same direction for all individuals. We say that \(X_1\) and \(X_2\) have positive monotonic effects on \(D\) if \(D_{1\omega}(\omega)\) is non-decreasing in \(x_1\) and \(x_2\) for all individuals \(\omega\), i.e., \(D_{1\omega}(\omega) \geq D_{1\omega'}(\omega)\) for \(\forall \omega\) whenever \(x_1 \geq x'_1\) and \(x_2 \geq x'_2\).\(^5\) Under the assumption of positive monotonic effect of \(X_1\) and \(X_2\), the individuals of response types 3, 5, 7, and 9 through 15 are excluded; and individuals of response types 1, 2, 4, 6, 8, and 16 may remain. These individuals can have, at the maximum, 446 risk-status patterns for the sufficient causes, including \(A_2X_1, A_2X_2, A_2X_1X_2, A_2X_1X_2, A_2X_1X_2, A_2X_1X_2\) and \(A_2X_1X_2\). By contrast, we will say that the assumption of no preventive action of \(X_1\) and \(X_2\) holds if sufficient causes \(A_2X_1, A_2X_2, A_2X_1X_2, A_2X_1X_2, A_2X_1X_2\), and \(A_2X_1X_2\) are all absent so that neither \(X_1\) nor \(X_2\) acts in a sufficient cause.\(^4\) These remaining individuals can have, at the maximum, 16 risk-status patterns for the sufficient causes. Therefore, the absence of \(X_1\) and \(X_2\) in any sufficient cause is stronger than the assumption of positive monotonic effects of both \(X_1\) and \(X_2\). Thus, the concepts of “positive monotonic effect” and “no preventive action” should be clearly distinguished; the former is defined in the potential-outcome framework, while the latter is defined in the sufficient-component cause framework. Recently, VanderWeele\(^6\) distinguished these concepts by using the terms “counterfactual monotonicity” and “sufficient-cause monotonicity,” respectively.

Consideration of the correspondence between the 2 models should allow greater insight to facilitate use of each model in the appropriate contexts, clarifying the strengths of each model. Our explication would also facilitate understanding of the recent findings on the identifiability of particular sufficient causes and response types.\(^5,7,8\) As the

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duality between the 2 models shows, the different approaches to causality provide complementary perspectives, and can be employed together to improve causal interpretations.

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**COLOR-CODED AUDIO COMPUTER-ASSISTED SELF-INTERVIEW FOR LOW-LITERACY POPULATIONS**

To the Editor:

Self-reported measures are widely used in epidemiologic research; however, the validity of such reports may be questionable when studying sensitive topics. Self-administration of surveys removes interviewer effects and may reduce social desirability bias, but at the cost of potential subject confusion or data-entry errors. Audio computer-assisted self-interview (ACASI) systems provide for a high level of confidentiality, while removing literacy barriers.

The power structure of prisons combines with a history of abusive research involving prisoners1 to create an environment where pressure to misreport may be especially high. Rates of illiteracy among prisoners are high,2 limiting the utility of self-administered paper surveys. We examined the performance of a color-coded ACASI system for gathering sensitive data from male prisoners.

The participants completed a questionnaire regarding their adverse childhood experiences exposure as part of a survey of prisoner tobacco use.3 The Ohio State University Institutional Review Board and Ohio Department of Rehabilitation and Corrections approved all procedures, and all subjects gave informed consent to participate. The survey covered 7 categories, including physical, emotional, and sexual abuse.4 We collected data on a laptop computer-based, color-coded ACASI system, programmed using Visual Basic for Applications within Microsoft Access 2000 (Microsoft Corporation, Redmond, WA). The system displayed the question and responses onscreen while participants heard an audio recording of the materials over headphones. For example: “How often did a parent, step-parent, or adult living in your home swear at you, insult you, or put you down? If never, press red. If once or twice, press orange. If sometimes, press yellow. If often, press green. If very often, press blue. To skip this question, press black. To hear it again, press white.”

Participants entered their responses using a customized data entry device with 7 color-coded keys, built by modifying a number pad (Figure). The program had participants confirm each answer. For example, “You chose ‘never.’ If this is correct, press black. To change your answer, press white.”

The interviewer remained present during a sample question to adjust volume settings and answer any participant questions, but moved out of sight during survey administration. Following confirmation of the final response, the program instructed the participant to notify the interviewer.

The questionnaire was completed by 198 of 200 eligible participants (99%). Item response rates were high among those who received the questionnaire (range: 98%–100%; median = 100%). Complete responses were received from 191 men (96%); 2 men (1%) declined to answer 1 question but provided sufficient information to determine exposure to adverse childhood events for all categories, and 5 men (3%) declined to answer one or more questions in a manner that made it impossible to definitively determine their exposure.

Nearly all participants were willing and able to answer questions using the color-coded ACASI system, regardless of their prior experience with computers or comfort with reading. Intake data, collected by the Ohio Department of Rehabilitation and Correction from “self admissions, social and criminal history records,” identified physical and abuse in 8% of male inmates and sexual abuse in 5%.5 When using the ACASI system, participants in the current study

**Color-coded Audio Computer-assisted Self-interview for Low-literacy Populations**

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reported about 3 times the prevalence of both physical (24%) and sexual (16%) abuse, possibly indicating a higher degree of comfort in sharing sensitive information when using the confidential system.

To promote dissemination of ACASI systems, the computer code used to create the system is available, for free, through the author’s website for use or modification by other researchers (http://publichealthresearch.org/FreeCASI), as are instructions for building a color-coded keypad. Color-coded ACASI systems, such as the one described in the present study, offer an effective means of gathering sensitive data, even when participants have difficulty reading or using computers.

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