Table 1. Definitions of Severe Disability According to the Extended Glasgow Outcome Scale and the Modified Rankin Scale.

Scale and Category	Definition
Extended Glasgow Outcome Scale	
Upper severe disability	Patient does not require assistance at home (or can be left alone for at least 8 hr) but requires assistance outside the home
Lower severe disability	Patient is dependent on others for care
Modified Rankin scale*	
Moderately severe disability (a score of 4)	Patient is unable to walk without assistance and unable to attend to his or her own bodily needs without assistance
Severe disability (a score of 5)	Patient is bedridden, incontinent, and requires constant nursing care and attention

* Scores on the modified Rankin scale, which assesses the degree of disability or dependence in daily activities, range from 0 (no symptoms) to 6 (death).

per severe disability is a better outcome than a modified Rankin score of 4 (on a scale from 0 [no symptoms] to 6 [death]), the threshold that has driven the use of craniectomy in patients with ischemic stroke (Table 1).[4]

Also, barbiturates were an option in patients in the medical group after randomization. The fact that 37.2% of patients in the medical group eventually underwent a craniectomy, whereas 9.4% of patients in the surgical group required barbiturates, indicates that the failure to control intracranial pressure was greater in the medical group.

We agree with Chesnut about the acceptability of disability but question the statement regarding "failed" trials. The DECRA trial and the European Study of Therapeutic Hypothermia (32°C–35°C) for Intracranial Pressure Reduction after Traumatic Brain Injury (the Eurotherm3235 Trial) were valuable because they showed that craniectomy and hypothermia, respectively, are not beneficial as stage 2 interventions. The progesterone trial by Wright et al., which was cited by Chesnut as a failed trial, did not address intracranial hypertension. We think that the treatment of intracranial hypertension will remain important, since it is a driver of increased mortality.[5] Integration of intracranial-pressure waveform analysis (in order to characterize autoregulation) with multimodality monitoring (microdialysis, brain oxygenation, and electrocorticography) can identify pathophysiological subgroups and may allow targeted treatment after TBI.

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Since publication of their article, the authors report no further potential conflict of interest.

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Dietary Sodium and Cardiovascular Disease Risk

TO THE EDITOR: Cogswell et al. (Aug. 11 issue)[1] argue that the reported association between low sodium intake and increased cardiovascular risk does not fulfill the criteria for causality, and they therefore conclude that low sodium intake should be recommended. We wish to call attention to several issues in their assessment of the available data.

First, the criticism by Cogswell et al. with regard to fasting urinary sodium estimates of

group-level sodium intake is misleading, because this method has been validated in a large international study (intraclass correlation vs. 24-hour urine samples, 0.71), has a similar association with blood pressure as that for sodium-intake estimates derived from 24-hour urine samples, and has been suggested by the World Health Organization (WHO) as a method of estimating sodium intake in populations. Furthermore, an increased risk of cardiovascular disease or death with low sodium intake is not confined to studies that use spot or fasting urinary estimates; studies that have used a variety of methods to measure sodium intake (including dietary assessments and 24-hour urine samples) in diverse populations have reached the same conclusion.[2] We recognize that the assessment of sodium intake in an individual person requires multiple 24-hour measurements, but that is not required to assess the association between categories of sodium intake and cardiovascular disease in populations.

Second, in their application of the Hill criteria, it is surprising that in a discussion of the plausibility criterion the authors would not include the fact that sodium is an essential mineral. J-shaped associations are expected and common for physiologic factors, such as other minerals (e.g., calcium), vitamins (e.g., vitamin D), and hormones (e.g., thyroxine). Sodium is essential to life and is required for cellular action potentials and volume balance. Although excess sodium intake is a risk factor for hypertension, low sodium intake activates the renin–angiotensin–aldosterone system and is a modifiable risk factor for orthostatic hypotension. We think that the suggestion that sodium intake can be very low and yet be entirely safe contradicts our understanding of the role of sodium in human physiology.

Third, the case presented by Cogswell et al. is predicated primarily on disproving the harm, rather than on establishing a cardiovascular benefit, of low sodium intake. It is not known whether low sodium intake results in a lower risk of cardiovascular disease than moderate sodium intake does, but there is generally consistent epidemiologic evidence that high sodium intake (>5 g per day) is associated with a higher risk of cardiovascular disease.[2] None of the studies referenced by Cogswell et al. show that the risk of cardiovascular disease with low sodium intake (<2.3 g per day) is significantly lower than the risk with moderate intake in general populations. They highlight two cohort studies to support their case,[3,4] but neither study showed that the risk of cardiovascular disease with an intake of less than 2.3 g per day was significantly lower than the risk with moderate intake ranges. One study describes a J-shaped association between sodium intake and the risk of myocardial infarction, with a nadir of risk of all cardiovascular disease events at a moderate sodium intake of 2.9 to 3.6 g per day,[4] findings that are entirely consistent with a J-shaped association shown in other prospective cohort studies. The interpretation by Cogswell et al. of a 2014 Cochrane review[5] contradicts the conclusions reached by the authors, with the latter reporting insufficient power to confirm clinically important effects. The authors reference an Institute of Medicine (IOM) review[6] as supporting a low sodium intake (<2.3 g per day), but it did not. The IOM committee found that the evidence from studies of direct health outcomes was insufficient and inconsistent for the conclusion that the lowering of sodium intake to below 2.3 g per day either increases or decreases the risk of cardiovascular disease, and it recommended better-quality cohort studies and randomized trials.

Proof of the benefit and safety of low sodium intake on health outcomes is needed before extreme reduction in sodium intake can be recommended for entire populations. Until large, randomized trials clearly show a lower risk of cardiovascular disease with low sodium intake, there is no solid basis for recommending low sodium intake for the prevention of cardiovascular disease. Current public health efforts should focus on reducing sodium intake in populations with high sodium intake (>5 g per day) rather than on diverting resources in the pursuit of an unproven strategy of low sodium intake for the entire population.

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TO THE EDITOR: The Centers for Disease Control and Prevention (CDC) commentary advises U.S. residents to limit dietary sodium to less than 2300 mg per day. This article misinterprets Hill's address to the Section of Occupational Medicine of the Royal Society of Medicine.[1] His focus was on decision making when clinical trials are unethical, such as in cases of exposure to toxic chemicals or air pollution. For everything else, Hill passionately advocated clinical trials.

The authors of the CDC commentary raise reasonable concerns about the methods and interpretation of some of the 33 relevant observational studies.[2] In 6 individual studies and a meta-analysis (14 studies involving a total of 100,000 participants), an intake of less than 2645 mg of sodium per day was associated with increased mortality.[2] But observational data cannot resolve clinical or public health questions — that requires experimental evidence. The CDC sponsored the 2013 IOM report that concluded that the available evidence is insufficient to determine whether a sodium intake of less than 2300 mg per day is harmful or helpful.[3] No conflicting evidence has emerged since.

Public health "action" cannot be justified by extrapolation from studies with intermediate end points, such as blood pressure, from expert opinion, or from a few of many observational studies. There is no substitute for reproducible clinical trials.[4]

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No potential conflict of interest relevant to this letter was reported.

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4. Evidence-based policy for salt reduction is needed. Lancet 2016;388:438.

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TO THE EDITOR: Cogswell et al. refer to a dose–response analysis that showed that an incremental reduction in sodium intake of 1000 mg per day was associated with an average decrease in systolic blood pressure of 1.7 mm Hg. This analysis used data from our Cochrane review.[1] Our own calculations show that this decrease is 1.0 mm Hg per 1000 mg decrease in the daily sodium intake. The analysis that produced the outcome of 1.7 mm Hg was based on an extrapolation through zero, although this approach is discouraged by the manual of the statistical software,[2] because it excludes confounding and measurement error. Furthermore, a separation of the overrepresented number of hypertensive study populations from the underrepresented number of normotensive study populations showed that the dose–response relationship in hypertensive persons is approximately 2.6 mm Hg per 1000 mg of sodium, but in normotensive persons it is approximately 0 mm Hg. Consequently, at least 70% of the U.S. population will have no benefit on blood pressure by reducing their sodium intake

but will, in contrast, have side effects.[1] Other studies have shown that a reduction in sodium intake increases mortality, especially among normotensive persons.[3] Consequently, a reduction in salt intake at the population level should not be a public health priority.[4]

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TO THE EDITOR: Cogswell and colleagues used Hill's causal criteria to assess the evidence relating low salt intake to an increased risk of cardiovascular disease and found the purported link unconvincing. But Hill championed other criteria that the authors did not consider. In an often-overlooked section of the same article, Hill discussed how decision makers can move from evidence to action in light of the potential consequences of error, and he argued for "differential standards" depending on the context. "Slight evidence" of risk, he said, might be enough to restrict the use of a drug to treat morning sickness in pregnant women, whereas "very strong evidence" should be required before moving to restrict people from "eating the fats and sugar that they do like."[1]

Does the case for salt reduction meet this high standard? The authors assert that "the evidence shows that sodium reduction prevents cardiovascular disease." But the 2015 Dietary Guidelines Advisory Committee found the strength of the evidence linking higher levels of sodium intake and risk of cardiovascular disease to be only moderate.[2] Other assessments are much less charitable.[3] Thus, it is not clear that salt reduction satisfies all Hill's criteria for preventive action.

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THE AUTHORS REPLY: O'Donnell and colleagues cite studies purporting to show increased mortality with low sodium intake, but many studies of sodium and health outcomes are deeply flawed by measurement error, confounding, and reverse causality.[1] For studies of cardiovascular disease outcomes, long-term diet, rather than intake on a single day or a small number of days, is the relevant measure of sodium intake.[2] Urinary sodium excretion varies enormously throughout the day, from day to day, and according to diet, medications, chronic diseases, and hormonal fluctuations; only multiple, complete, 24-hour urine samples accurately reflect the usual sodium intake in an individual person.[1,2] Estimates of 24-hour sodium excretion that are based on spot urine samples, and therefore the apparent association between cardiovascular disease outcomes and spot urine samples, can be substantially biased.[3] Analysis without multiple 24-hour urine samples inaccurately categorizes sodium intake for many persons and contributes to an ostensible but invalid J-shaped association with cardiovascular disease in individual studies or in meta-analyses such as that cited by Alderman. In contrast, the use of multiple 24-hour urine collections indicates a positive and linear, not J-shaped, association with total mortality across a broad range of sodium intake, including among participants whose usual sodium intake was less than 2300 mg per day.[4]

In response to O'Donnell et al. and Graudal: the combination of trials with widely varying levels and durations of intended or achieved reduction in sodium intake may bias results. Clinical trials typically analyze sodium exposure on the basis of the intention-to-treat principle; if

participants do not meet target reductions (e.g., because the food environment makes low sodium consumption extremely difficult), results are biased toward the null. Also, extreme, rapid reductions (e.g., down to levels below physiologic need, <500 mg) do not reflect the effects of long-term, moderate population-wide reductions in sodium intake such as those proposed by the Food and Drug Administration. According to a Cochrane review of 34 randomized trials involving normotensive participants and hypertensive participants, moderate and longer-term (>4 weeks) reduction in sodium intake, down to less than 1500 mg daily, significantly lowers blood pressure in a linear dose–response relationship; the effects on the renin–angiotensin–aldosterone system are small and within the expected physiologic range.[5] In a meta-analysis of long-term randomized trials, the effects of average reductions of 400 to 1200 mg in daily sodium intake significantly reduce the risk of cardiovascular events by 20% among normotensive participants and hypertensive participants combined, with a reduction of similar magnitude, albeit with inadequate sample size to show statistical significance, among the subgroup of normotensive participants.[6]

In response to O'Donnell et al., Alderman, and Johns: Hill's causal criteria focused on occupational hazards and preventive medicine and included examples that were related to cigarette smoking and diet. Hill stated that requiring strong evidence "does not imply crossing every 't' and swords with every critic, before we act." He concluded that "all scientific work is incomplete — whether it be observational or experimental" and emphasized not ignoring the knowledge we have. A general population trial to determine cardiovascular outcomes is impractical, because it would require tens of thousands of persons to maintain intended dietary sodium levels for many years.[6]

The 2013 IOM committee concluded, "Although the reviewed evidence on associations between sodium intake and direct health outcomes has methodological flaws and limitations . . . when considered collectively, it indicates a positive relationship between higher levels of sodium intake and CVD risk. This evidence is consistent with existing evidence on blood pressure as a surrogate indicator of CVD risk." To correct misinterpretation, the IOM committee chair wrote, "Rather than focusing on disagreements about specific targets that currently affect less than 10% of the U.S. population (i.e., sodium intake of <2,300 mg/d vs. <1,500 mg/d), the IOM, AHA, WHO, and DGA [*Dietary Guidelines for Americans*] are congruent in suggesting that excess sodium intake should be reduced." The 2015 Dietary Guidelines Advisory Committee, noting general population goals of less than 2300 mg of sodium per day, concluded that the totality of evidence of a cardiovascular benefit from limiting dietary sodium is strong and encouraged the food industry to reduce the amount of sodium added to foods in order to support healthy dietary choices.

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