In our opinion, there are other relevant considerations:

1. The study population is at very low risk of stroke (number of observed events = 183 during a follow-up of more than 12 years), with a prevalence of 0.21% per year, in front of the actual stroke prevalence of 0.8% to 8.2 % per year (from 4x to 40x) in the general population across Europe.[4,5]
2. The group in the lowest quintile of UNaV has an average value of 83 mmol per 24 hours (really low; actually well below the current indications). In this group, the possible reverse causality should be investigated.
3. The patients with the lowest UNaV show also the lowest potassium excretion, reflecting a low potassium intake. High potassium intake has protective cardiovascular effects. This is not taken into account in the discussion.
4. In Figures A and B of their study,[1] Kieneker et al report graphically the inverse (J-shaped?) relationship between UNaV and risk of stroke, after adjusting (A) for age and sex, and (B) additionally adjusting for height, weight, race, smoking status, and so on, but not for blood pressure and/or antihypertensive medication consumption, although these last adjustments may have clarified their findings.

In our opinion, the paper by Kieneker et al [1] is the first to have addressed correctly a possible inverse relation between sodium intake and risk of stroke; their conclusions are nevertheless clouded by a number of confounders.

Natale Musso, MD
Andrea Dotto, MD
Department of Internal Medicine
IRCCS Policlinico San Martino Genova
Italy

Potential Competing Interests: The authors report no competing interests.

1. Kieneker LM, Eisenga MF, Gansevoort RT, et al. Association of low urinary sodium excretion with increased risk of stroke. *Mayo Clin Proc.* 2018; 93(12):1803-1809.
2. O'Donnell M, Mente A, Rangarajan S, et al; PURE Investigators. Urinary sodium and potassium excretion, mortality, and cardiovascular events (Published correction appears in *N Engl J Med.* 2014;371(13): 1267.). *N Engl J Med.* 2014;371(7):612-623.
3. Campbell NRC. Dissidents and dietary sodium: concerns about the commentary by O'Donnell et al. *Int J Epidemiol.* 2017;46(1):362-366.
4. The burden of stroke in Europe. King's College of London, SAFE Secretariat. Stroke Association House, http://strokeeurope.eu/index/the-burden-of-stroke-in-europe/. Accessed September 29, 2018.
5. Béjot Y, Bailly H, Durier J, Giroud M. Epidemiology of stroke in Europe and trends for the 21st century. *Presse Med.* 2016;45(12):e391-e398.

https://doi.org/10.1016/j.mayocp.2018.12.027

In reply—Low-Sodium Intake: A Risk Factor for Stroke?

To the Editor: We are grateful to Drs Musso and Dotto[1] for the appraisal of our article on low urinary sodium excretion (UNaV) as an indicator of low sodium intake and increased risk of stroke.[2] We agree that the mentioned earlier study by O'Donnell and colleagues,[3] although representative of various populations by including more than 100,000 participants from 17 countries, has some limitations. In particular, the assessment of sodium intake via a single spot urine sample is a major limitation. Actual measurement of 24-hour UNaV in multiple urine collections (to account for day-to-day variability), as we did in the Prevention of Renal and Vascular End-Stage Disease (PREVEND) study, has been shown to be a more accurate method for the assessment of usual sodium intake.[4,5]

In their letter, Drs Musso and Dotto note potential concerns regarding our study. First, they noted that the number of strokes among the participants of PREVEND study is low when compared with other European populations. For this, it is important to realize that, in our study, we excluded all participants with cardiovascular events (including strokes) at baseline. Therefore, in our analyses we are investigating incidence rates of stroke rather than rates of prevalence. But, still, the stroke incidence rate of 0.21% per year in the PREVEND study may seem relatively low compared with the incidence rates of other European populations, which reportedly range from 0.08% to 2.54%, with highest rates in Eastern and Northern Europe (Croatia, Estonia, Lithuania, Sweden).[6] These differences among countries can partly be explained by the presence of risk factors of stroke such as the number of smokers, elevated blood pressure, elevated cholesterol levels, and treatment of stroke. However, some of this variation is likely also due to the different criteria—such as inclusion of transient ischemic attacks—and methods used to collect the data.[7] Important to note is that the incidence of stroke in the PREVEND study (0.21% per year) is very similar to the overall stroke incidence reported for the Netherlands (0.23% per year).[8]

Second, the participants of the PREVEND study had relatively low sodium intake when compared with other study populations.[9] When looking at the lowest quintile of UNaV, we observed that the median intake of this quintile was 83 mmol per 24 hours. Assuming that approximately 90% of ingested sodium is excreted in the urine,[4] subjects in this lowest quintile of UNaV consumed approximately 5.4 grams of salt per day (equivalent to 92 mmol of sodium per day). This is slightly below the current

recommendation for maximum salt intake of 6.0 grams of salt per day set by the Dutch Health Council[10] and slightly above the recommendation for a maximum intake of 5.0 grams of salt per day set by the World Health Organization.[11] However, when comparing the median intake of the PREVEND study of 8 grams per day (equivalent to 137 mmol of sodium per day) with the global mean intake of salt of approximately 10 grams per day (equivalent to 168 mmol of sodium per day),[9] we can conclude that the intake of sodium in the PREVEND study is relatively low. One might suppose that the association observed between low intake of sodium and risk of stroke may be explained by reverse causality, wherein a change in dietary choices is prompted by disease status. However, at baseline we already excluded subjects with history of cardiovascular disease, and, in sensitivity analyses, we tried to limit the chance of reverse causality by excluding all subjects with malignancies, type 2 diabetes, and chronic kidney disease at baseline. Exclusion of these patients did not materially change the results (hazard ratio [HR] per 1 standard deviation [SD] [51 mmol/24h] decrement, 1.45; 95% confidence interval [CI], 1.10-1.92), making reverse causality unlikely. However, as our study is observational in nature, reverse causality cannot completely be ruled out.

Third, we agree with Drs Musso and Dotto that sodium intake is closely linked to potassium intake and that high potassium has protective cardiovascular effects. For this reason, we included 24-hour urinary potassium excretion as a marker of potassium intake and as a potential confounder in the survival analyses (multivariable adjusted model 3). The association of low sodium intake with increased risk of stroke remained independent of adjustment for urinary potassium excretion (HR per 1 SD [51 mmol/24h] decrement, 1.44; 95% CI, 1.14-1.82), supporting the notion that the increased risk of stroke observed is not due to harm induced by low potassium intake.

Fourth, the same holds true for adjustments for blood pressure and use of antihypertensive medication. We examined whether these variables were potential mediators of the association between sodium intake and stroke by including these variables in the multivariable model. However, the association of UNaV with risk of stroke remained materially unchanged (HR per 1 SD [51 mmol/24h] decrement, 1.47; 95% CI, 1.14-1.89). We therefore did not include these variables in the model on which Figure 1 is based, as these variables did not materially influence the association between urinary sodium intake and risk of stroke.

We thank Drs Musso and Dotto for appraising our paper as the first to correctly address a possible inverse association between sodium intake and risk of stroke and agree that, as in any study of observational nature, a risk of residual confounding will remain. As Drs Musso and Dotto implicitly suggest, more and higher-quality evidence on potential harmful effects of low sodium intake is certainly needed.

Lyanne M. Kieneker, PhD
Michele F. Eisenga, MD
Stephan J.L. Bakker, MD, PhD
Department of Internal Medicine
University Medical Center
University of Groningen
The Netherlands

Potential Competing Interests: The authors report no competing interests.

1. Musso N, Dotto A. Low-sodium intake: a risk factor for stroke? *Mayo Clin Proc*. 2019;94(4):728-729.
2. Kieneker LM, Eisenga MF, Gansevoort RT, et al. Association of low urinary sodium excretion with increased risk of stroke. *Mayo Clin Proc*. 2018;93(12):1803-1809.
3. O'Donnell M, Mente A, Rangarajan S, et al. Urinary sodium and potassium excretion, mortality, and cardiovascular events. *N Engl J Med*. 2014;371(7):612-623.
4. Holbrook JT, Patterson KY, Bodner JE, et al. Sodium and potassium intake and balance in adults consuming self-selected diets. *Am J Clin Nutr*. 1984;40(4):786-793.
5. McLean RM. Measuring population sodium intake: a review of methods. *Nutrients*. 2014;6(11):4651-4662.
6. King's College of London. The burden of stroke in Europe. http://strokeeurope.eu/index/the-burden-of-stroke-in-europe. Accessed October 23, 2018.
7. Levi F, Chatenoud L, Bertuccio P, Lucchini F, Negri E, La Vecchia C. Mortality from cardiovascular and cerebrovascular diseases in Europe and other areas of the world: an update. *Eur J Cardiovasc Prev Rehabil*. 2009;16(3):333-350.
8. Rijksinstituut voor Volksgezondheid en Milieu (RIVM). Prevalentie en nieuwe gevallen van beroerte. https://www.volksgezondheidenzorg.info/onderwerp/beroerte/cijfers-context/huidige-situatie#node-prevalentie-en-nieuwe-gevallen-van-beroerte. Accessed October 23, 2018.
9. Powles J, Fahimi S, Micha R, et al. Global, regional and national sodium intakes in 1990 and 2010: a systematic analysis of 24 h urinary sodium excretion and dietary surveys worldwide. *BMJ Open*. 2013;3(12). e003733-2013-003733.
10. Gezondheidsraad. *Natrium: Achtergronddocument bij Richtlijnen goede voeding 2015* 2015. A15/15.
11. World Health Organization. *Guideline: Sodium Intake for Adults and Children*. Geneva, Switzerland 2012.

https://doi.org/10.1016/j.mayocp.2018.12.026

Mona Lisa Decrypted: Another Premise

To the Editor: In the September 2018 issue of *Mayo Clinic Proceedings*, Mehra and Campbell[1] gave a lovely and elegant review of the Mona Lisa painting and posited a medical explanation for the mystery of the lady as painted by the great master Leonardo da Vinci. Their insights tied hypothyroidism with attendant hyperlipidemia, lipoma, and xanthelasma as the cause of the enigmatic smile and her gaze. There is merit to this diagnosis, and this should be heavily weighted in the differential diagnosis analysis. Other analysts have attributed this to neurosyphilis,[2] postpartum Bell's palsy,[3] dentition