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THE AUTHORS REPLY: We welcome vigorous debate about all aspects of assessment of health system performance, with the ultimate goal of improving the health of populations. The World Health Report 2000[1] generated a rich discussion that advanced this field of study enormously, leading to a 927-page volume published by the WHO in 2003[2] and feeding into health care reform initiatives in China, Mexico, Iran, and elsewhere.

Musgrove criticizes our Perspective article for citing rankings from the 2000 report. It is important to note that he was one of the report's lead authors and that 3 years after its publication, he took the unusual step of critiquing his own report.[3] At that time, we published a thorough rebuttal.[4]

The United States spends more on health care and yet has worse rates of death and a higher disease burden than countries that spend far less. Apologists for the U.S. system tend to ignore these facts and attempt to distract observers from the real challenges the country faces. If we do not build a strong evaluation component into reform, we will miss opportunities for learning through implementation, correcting the course if needed, promoting accountability, and mustering public support. Unfortunately, on these critical points, Musgrove is silent.

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

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Failure to Validate Association between 12p13 Variants and Ischemic Stroke

TO THE EDITOR: Recently published data from a meta-analysis of genomewide association studies showed that two common single-nucleotide polymorphisms (SNPs) near the *NINJ2* and *WNK1* genes on chromosome 12p13 were associated with ischemic and, in particular, atherothrombotic strokes.[1] To validate these results, we conducted a meta-analysis in a combined sample of 8637 cases and 8733 controls of European ancestry, as well as one population-based genomewide cohort study of 278 ischemic strokes among 22,054 participants.

Both SNPs from the original report (rs12425791 and rs11833579) were tested for association with ischemic stroke, as well as incident stroke, recurrent stroke, and stroke subtypes (according to the Trial of Org 10172 in Acute Stroke Treatment [TOAST] criteria[2]). We also conducted similar analyses in cases and controls of African-American ancestry and in samples from Chinese and Pakistani subjects. Furthermore, we evaluated gene expression for *NINJ2* and *WNK1* in 132 cases with ischemic stroke and in 80 controls, as well as the association of the chromosome 12p13 variants with the risk of hemorrhagic stroke. Details regarding the study design and extended results are available in the Supplementary Appendix, available with the full text of this letter at NEJM.org.

We found no association between rs12425791 and ischemic stroke (odds ratio, 0.97; 95% confidence interval [CI], 0.91 to 1.04; P=0.41) or between rs11833579 and ischemic stroke (odds ratio, 1.02; 95% CI, 0.95 to 1.10; P=0.55) in persons of European ancestry (Fig. 1). We found no association between either of the SNPs and atherothrombotic stroke in 2235 cases (P>0.10) (Fig. 2) and no association between either of the SNPs and incident ischemic stroke, recurrent ischemic stroke, and ischemic stroke subtypes (P>0.10 for all comparisons). The power to detect an association at an effect size below the lower limit of the 95% confidence interval surrounding the original estimate exceeded 99% for ischemic as well as atherothrombotic stroke. We observed no differences in gene expression between cases and controls and no association between either of the SNPs and a risk of hemorrhagic stroke. Heterogeneity in meta-analyses of our studies was

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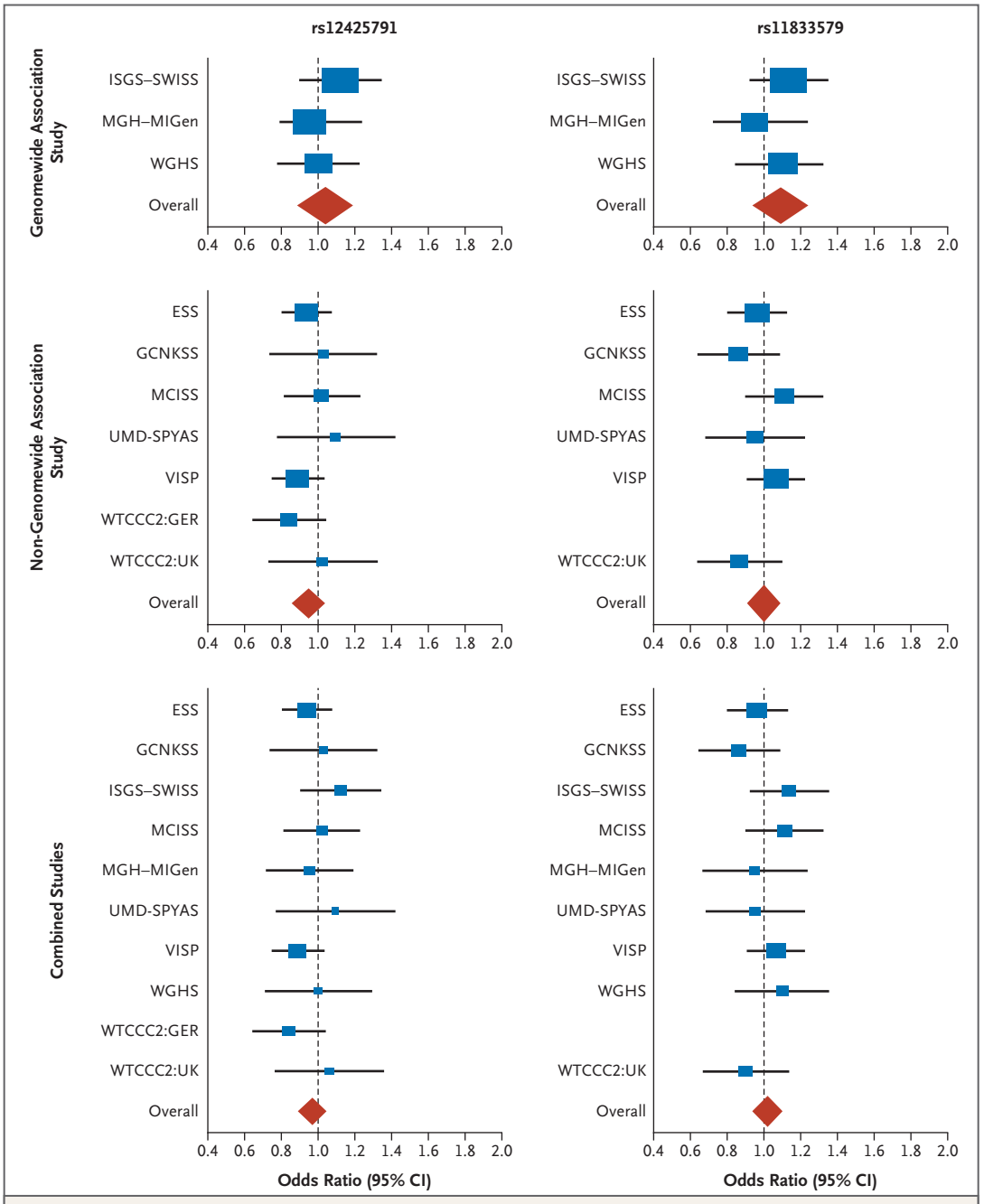

Figure 1. Associations between Single-Nucleotide Polymorphisms (SNPs) and Ischemic Strokes in Persons of European Ancestry, According to Study.

The forest plots show the odds ratios for the association between ischemic strokes and the minor allele (A) of both SNPs. No risk effect of these alleles was detected for either SNP. Data from 8915 persons with ischemic strokes are shown. The comparison group is 30,510 stroke-free controls. Individual studies (blue boxes) are plotted against the individual effect sizes (odds ratios). The red diamonds indicate overall odds ratios. The size of the blue boxes indicates study-specific weights for the meta-analysis. Horizontal lines indicate 95% confidence intervals. The dashed vertical line shows the lack of any effect on the risk of stroke (odds ratio, 1.0). ESS denotes Edinburgh Stroke Study, GCNKSS Greater Cincinnati/Northern Kentucky Stroke Study, ISGS Ischemic Stroke Genetics Study, MCISS Middlesex County Ischemic Stroke Study, MGH Massachusetts General Hospital, MIGen Myocardial Infarction Genetics Consortium, SWISS Siblings with Ischemic Stroke Study, UMD-SPYAS University of Maryland Stroke Prevention in the Young Study, VISP Vitamin Intervention for Stroke Prevention Trial, WGHS Women's Genome Health Study, WTCCC2:GER Wellcome Trust Case–Control Consortium 2, German data, and WTCCC2:UK Wellcome Trust Case–Control Consortium 2, United Kingdom data.

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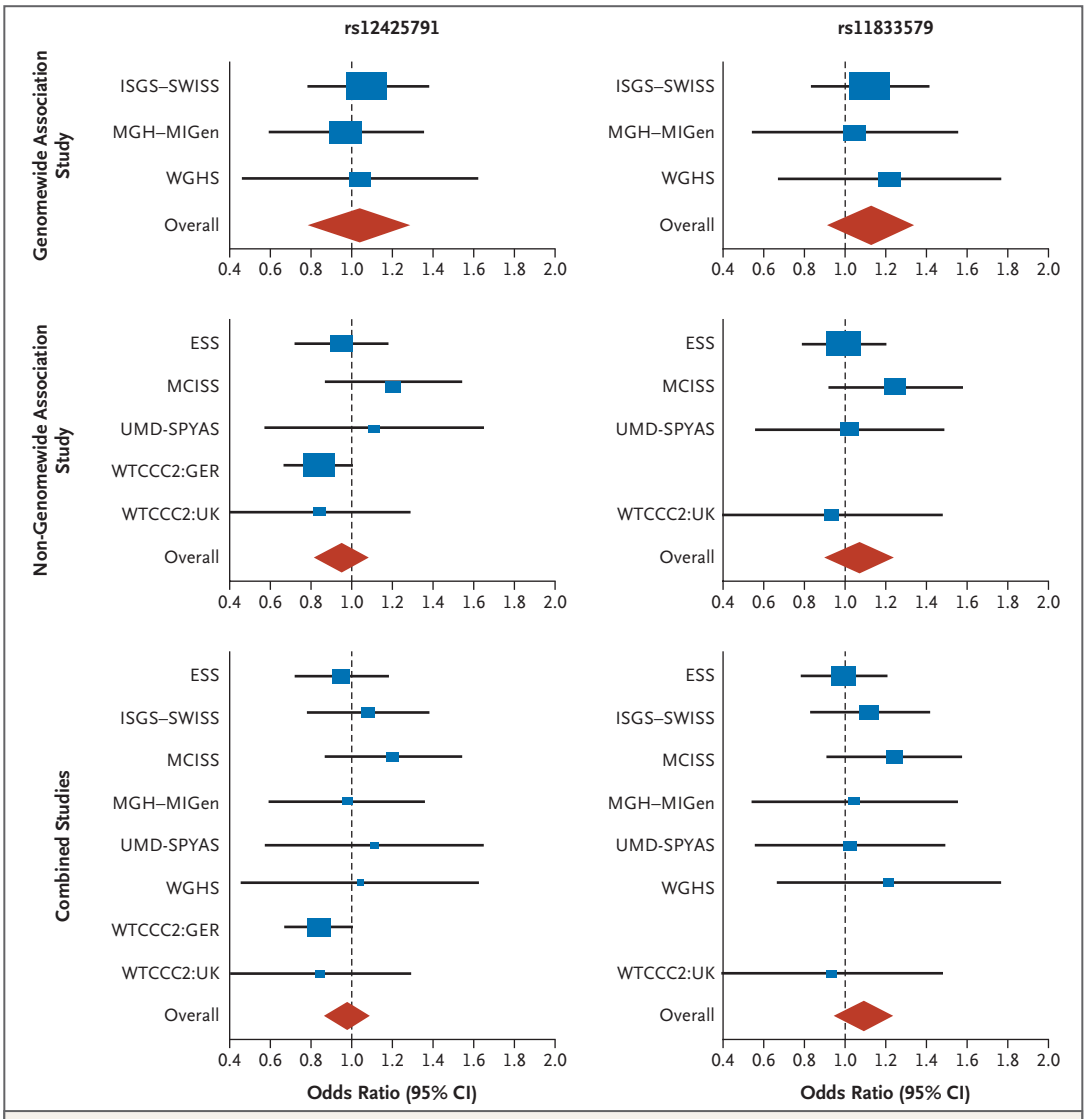

Figure 2. Associations between Single-Nucleotide Polymorphisms (SNPs) and Atherothrombotic Strokes in Persons of European Ancestry, According to Study.

The forest plots show the odds ratios for the association between atherothrombotic strokes and the minor allele (A) of both SNPs. No risk effect of these alleles was detected for either SNP. Data from 2235 persons with atherothrombotic strokes are shown. The comparison group is 30,510 stroke-free controls. Individual studies (blue boxes) are plotted against the individual effect sizes (odds ratios). The red diamonds indicate overall odds ratios. The size of the blue boxes indicates study-specific weights for the meta-analysis. Horizontal lines indicate 95% confidence intervals. The dashed vertical line shows the lack of any effect on the risk of stroke (odds ratio, 1.0).

not significant (P>0.20 for heterogeneity, proportion of total variation in study estimates because of heterogeneity in the meta-analysis [I^2 <20%),[3] although we did identify significant heterogeneity in the original report's meta-analyses for rs11833579 (P=0.07 for heterogeneity, I^2=56.1%) and rs12425791 (P=0.15 for heterogeneity, I^2=42.1%).[1]

Our well-powered meta-analyses did not validate previously reported associations between two SNPs (rs12425791 and rs11833579) and stroke.[1] This lack of validation is most likely because of a false positive result in the previous meta-analysis. Differences between our predominantly case–control sample and the cohort sample of the original study may also have been factors. Given the power of our meta-analysis, a false negative finding is unlikely. Our results strongly suggest

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that these SNPs do not confer a substantial, generalizable risk for ischemic stroke.

International Stroke Genetics Consortium and Wellcome Trust Case–Control Consortium 2

Individual investigators are listed in the Supplementary Appendix.

Representatives of the consortium (Jonathan Rosand, M.D. [Massachusetts General Hospital, Boston], James F. Meschia, M.D. [Mayo Clinic, Jacksonville, FL], and Andrew B. Singleton, Ph.D. [National Institute on Aging, Bethesda, MD]) assume responsibility for the overall content and integrity of the letter.

Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

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Autologous Pancreatic Islet Transplantation for Severe Trauma

TO THE EDITOR: Autologous pancreatic islet transplantation has been successfully carried out after total pancreatectomy for chronic pancreatitis, and allogeneic islet-cell transplantation has had limited success.[1,2] We report a case of successful islet transplantation from the pancreas after total pancreatectomy because of trauma.

A 21-year-old airman serving in a remote part of Afghanistan was hit by three high-velocity bullets on November 21, 2009, and was rapidly transferred to Walter Reed Army Medical Center. As part of needed rescue surgery, a portion of the stomach, the gallbladder, the entire duodenum, and the head of the pancreas were removed. In addition, the patient required left hemicolectomy and resection of a portion of the small bowel.

During the attempt to reconstruct the intraabdominal structures, the remnant pancreas (weighing 63.5 g, approximately half the entire pancreas) was found to be damaged from the effects of the gunshot wounds and was leaking pancreatic enzymes and dissolving critical abdominal structures and blood vessels. We decided to remove the entire remaining pancreas to prevent further leakage, breakdown, and bleeding, which could be fatal. The pancreas was flushed with University of Wisconsin solution, packed in ice, and transported to the University of Miami. The islets (221,250 islet equivalents of 40% purity and 90% viability) were shipped back to Walter Reed, where by laparotomy they were injected back into the patient's main portal vein so as to seed in the liver. Portal pressures remained normal throughout the infusion.

Levels of C-peptide in basal and stimulated (after an oral glucose-tolerance test) conditions were 0.5 ng per milliliter with a glucose level of 80 mg per deciliter (fasting) and 3.9 ng per milliliter with a glucose level of 184 mg per deciliter (stimulated). As of postoperative day 114, the patient had normal islet function. Liver enzymes peaked on day 3 (800 IU for aspartate aminotransferase and 900 IU for alanine aminotransferase) and normalized on day 8. The patient was able to discontinue insulin on day 24. Initially, he required a small amount of insulin (1 to 2 units per hour) for total parenteral nutrition and 11 serial surgical procedures to close his abdomen. As of day 20, the patient was eating a normal diet.

In this patient, we were able to isolate and transplant insulin-producing cells after a severe trauma requiring complete removal of the pancreas. This procedure may prevent diabetes and secondary complications if even a small portion of pancreas can be salvaged. We also showed the feasibility of sending a pancreas to a remote location for islet isolation and purification and then transporting the islets back for successful infusion within 24 hours.[3]

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Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

The views expressed in this letter are those of the authors and do not reflect the official policy of the Department of the Army, Department of the Navy, Department of Defense, or U.S. government.

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