American Journal of Epidemiology

Vol. 181, No. 7
DOI: 10.1093/aje/kwu319
Advance Access publication:
March 1, 2015

Systematic Reviews and Meta- and Pooled Analyses

The Contribution of Genomic Research to Explaining Racial Disparities in Cardiovascular Disease: A Systematic Review

Jay S. Kaufman*, Lena Dolman, Dinela Rushani, and Richard S. Cooper

* Correspondence to Dr. Jay S. Kaufman, Canada Research Chair in Health Disparities, Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, 1020 Pine Avenue West, Montreal, Quebec H3A 1A2, Canada (e-mail: jay.kaufman@mcgill.ca).

Initially submitted July 7, 2014; accepted for publication October 9, 2014.

After nearly a decade of genome-wide association studies, no assessment has yet been made of their contribution toward an explanation of the most prominent racial health disparities observed at the population level. We examined populations of African and European ancestry and focused on cardiovascular diseases, which are collectively the largest contributor to the racial mortality gap. We conducted a systematic search for review articles and meta-analyses published in 2007–2013 in which genetic data from both populations were available. We identified 68 articles relevant to this question; however, few reported significant associations in both racial groups, with just 3 variants meeting study-specific significance criteria. For most outcomes, there were too few estimates for quantitative summarization, but when summarization was possible, racial group did not contribute to heterogeneity. Most associations reported from genome-wide searches were small, difficult to replicate, and in no consistent direction that favored one racial group or another. Although the substantial investment in this technology might have produced clinical advances, it has thus far made little or no contribution to our understanding of population-level racial health disparities in cardiovascular disease.

cardiovascular disease; continental population groups; genomics; health-care disparities; systematic review

Abbreviations: CVD, cardiovascular disease; GWAS, genome-wide association study; SNP, single nucleotide polymorphism.

Epidemiologic research seeks to describe and explain patterns of disease in populations and to elucidate mechanisms that lead to successful public health or clinical interventions. Within multiethnic societies, racial disparities have long been viewed as both a scientific opportunity and a social injustice. The opportunity arises when health inequality between groups leads to the discovery of preventive interventions through the identification of noxious environmental, dietary, or occupational factors (1). The social injustice that must be confronted is the rate of premature disease and death that results from discrimination and inequality (2). A counter-narrative also exists, however, in which racial patterns in disease are seen as neither clues toward intervention nor indications of social injustice, but merely as an expression of intrinsic biologic variations among human subpopulations (3). Through this lens, subgroup differences might reflect local environmental adaptations, like sickle cell to endemic malaria (4), and therefore reveal physiologic mechanisms that inform therapies. Accordingly, the racial gap would be something intrinsic, not imposed by social inequality. Balancing the claims of these competing frameworks recapitulates the centuries-old "nature versus nurture" debate, and many scholars have noted that the mainstream view in clinical journals leans heavily on the "nature" side of this divide (5, 6). Biomedical essentialism waned somewhat by the end of the 20th century (7), but with the advent of molecular epidemiology and the Human Genome Project, it has once again become the dominant paradigm of the past 15 years (8, 9).

Although molecular techniques reinvigorated genetic hypotheses for the etiology of observed disparities, they also posed a distinct challenge to traditional epidemiologic methods. With the technology to directly measure genotype, one could no longer justify attributing causation to vaguely hypothesized genetic factors (10). Previously, authors would often observe a disparity, adjust statistically for measured social or behavioral factors, and conclude that the remaining disparity

was the genetic portion (11). Because measurements of environmental factors are typically crude, the residual disparity that formed this estimated genetic contribution was usually large (12). However, once DNA could be measured directly, the analysis had to proceed in the other direction, demonstrating how measured genetic variants could explain observed disparities in disease outcomes.

With the widespread recognition of "missing heritability" in genomic studies (13), the nature versus nurture dichotomy has largely been abandoned in favor of causal processes that are interactive, for example, via epigenetic mechanisms. The critique of simplistic genetic explanations is by no means new (14), yet the logical weakness of the binary worldview does little to constrain its continued application in practice. For example, a recent article in the *Journal of the American Medical Association* in which the authors explored racial differences in the association between serum vitamin D and coronary heart disease concluded, ". . . we are unable to discern characteristics that could conceivably cause differential confounding by race . . . Therefore, our data suggest that biological differences explain much of the observed heterogeneity" (15, p. 184). This indirect method of adjusting for measured environmental factors and attributing the residual disparity to intrinsic racial traits rests entirely on additive decomposition between genetic and environmental causes. This represents a striking disconnect between the conceptual framework currently accepted in the field and the actual behavior of scientists interpreting empirical results. Indeed, despite repeated reminders that heritability does not refer to the degree to which a trait is due to genetic versus environmental factors (16, 17), it is most often interpreted in exactly this way, producing a steady succession of published claims that a large proportion of a given disparity has a genetic explanation.

The first genome-wide association study (GWAS) was published approximately a decade ago, and more than 1,700 have now been conducted, cataloging over 4,000 single nucleotide polymorphisms (SNPs) in relation to over 200 disease phenotypes (18, 19). It was reported in 2008 that worldwide spending on genomic research was approximately $3 billion per year, with approximately $1 billion annually from the United States (20). The expectation is that this enormous social investment will yield causal variants that will reveal genetic mechanisms of disease as targets of population screening, prevention, and clinical or pharmacologic therapy (21). If any of these newly discovered causal variants have differential prevalence across continental populations, as a result of selection, drift, or founder effects, then they would presumably provide the kind of concrete explanatory mechanisms for observed disparities that are so often invoked speculatively in the literature.

In 2008, life expectancy at birth in the United States was 76.2 years for non-Hispanic white men and 70.8 years for non-Hispanic black men, whereas for women, the values were 81.2 and 77.5 years, respectively (22). The resulting mortality disparities are 5.4 and 3.7 years for men and women, respectively. For both sexes, cardiovascular diseases (CVDs) made the largest contribution, accounting for 32% (1.8 years) of the gap in men and 43% (1.6 years) in women. Mortality rates from stroke and heart disease are approximately 1.5 and 1.2 times higher, respectively, in blacks (23), whereas diagnosis of heart failure is approximately 50% higher (24), and the rate of venous thromboembolism is 30%–60% higher (25, 26). Hypertension occurs more often, at an earlier age (27), and with greater severity in blacks (28) and is associated with an approximately 3 times greater likelihood of death (29). Although various environmental and social factors certainly contribute to these disparities, a genetic basis for these profound disparities is most often asserted in the biomedical literature (30). We therefore focused on CVD in the present article. Our aim was to systematically examine published reviews and meta-analyses for direct evidence of genetic explanations for the observed disparities.

METHODS

We performed an electronic literature search through the PubMed database to identify review articles and meta-analyses related to genetic risk factors for CVD in samples that included populations of African ancestry. Review articles and pooled studies indexed in PubMed, rather than original reports, were targeted to retrieve a more stable set with a lower proportion of unreplicated associations from small samples (31). We focused our search on the 7-year period from January 1, 2007, to January 1, 2014, which corresponded to the rapid proliferation of large pooled GWAS activity. We allowed for the inclusion of a broad range of CVDs, including stroke, hypertension, and heart disease, as well as continuous measures of blood pressure. The complete search is shown in Web Appendix 1 (available at http://aje.oxfordjournals.org/).

This search strategy yielded 197 articles (Figure 1). The title and abstract of each article were reviewed, and we retained all publications that focused on appropriate disease outcomes and population, regardless of language. A total of 68 articles (Web Appendix 2) met these requirements and were read in full. Subsequently, 9 articles were excluded for having the wrong outcome, 3 for including populations that were neither European nor African in origin, and 9 for lacking of any specific genetic data. After these exclusions, there remained 47 articles relevant to the primary research question concerning genetic factors that might contribute to disparities in CVD incidence or mortality and that compared populations of European and African ancestry.

Data from all 47 relevant articles were summarized and tabulated, with the following information extracted when available: study year; study design; outcome; sample sizes by group; number of SNPs investigated; gene names and RefSNP (rs) accession numbers; genetic model used; significance threshold *P* value used; effect measure estimated; variant location and nearby genes; allele and genotype frequencies by group; and whether the article provided any assertion that genetic factors provided an explanation for racial/ethnic disease disparities. All reported associations that exceeded the study's stated threshold *P* values were included as positive findings. Additionally, because many studies reported several effect estimates for a given variant, based on a variety of genetic models, we retained the estimate that corresponded to the most extreme genotype possibility representing presence versus absence of the susceptibility allele. If carrier frequencies were not reported in the articles, approximate allele frequency data were obtained from the HapMap database CEU (for

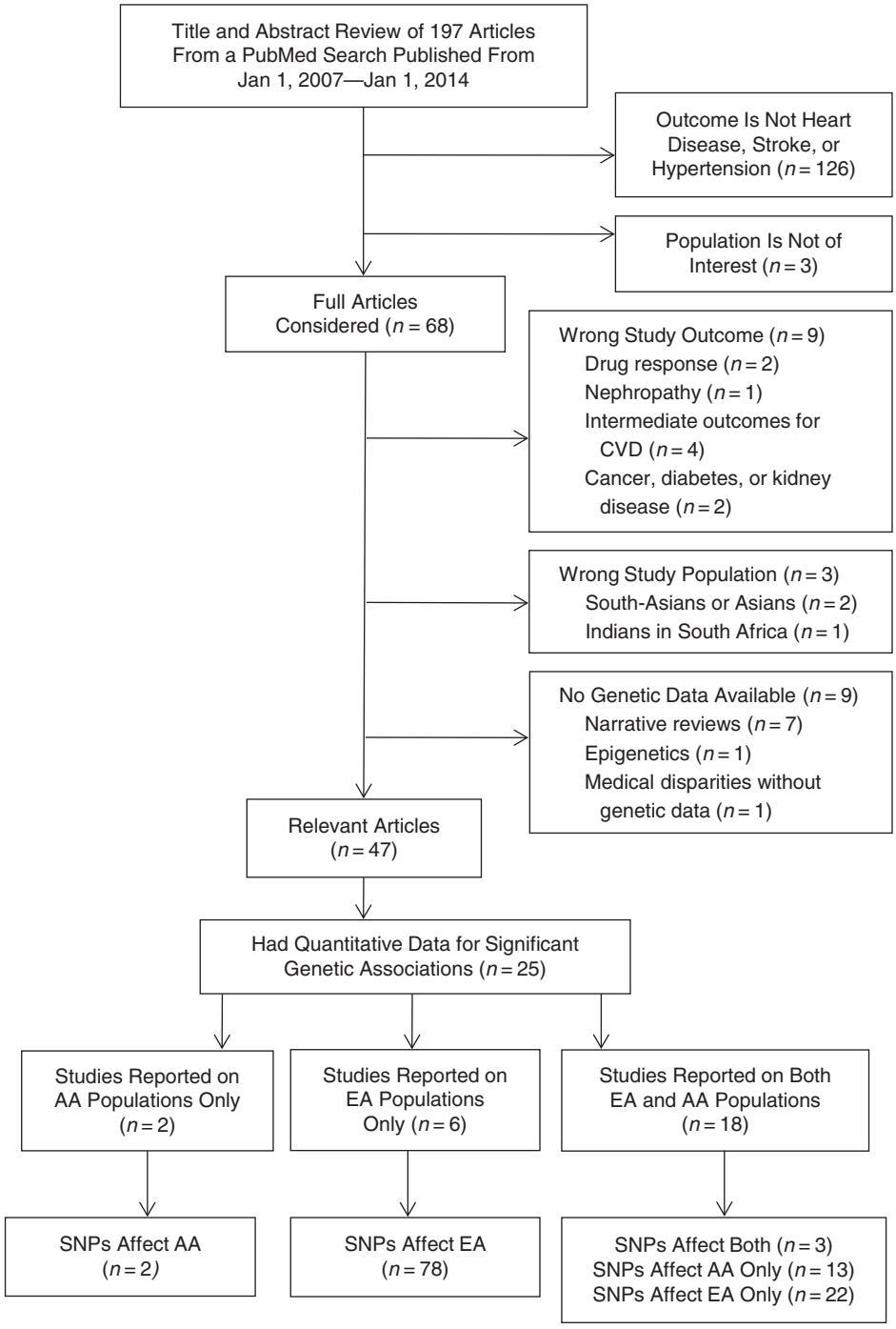

Figure 1. Flowchart of literature search strategy and exclusion criteria. In 1 article (64), the authors reviewed data from studies of European ancestry (EA) cohorts only and studies that included both EA and African ancestry (AA) cohorts. That article is therefore counted twice in the flowchart: once in the studies on EA only ($n = 6$) and once in the studies on both EA and AA ($n = 18$). CVD, cardiovascular disease; SNPs, single nucleotide polymorphisms.

European ancestry) or YRI (for African ancestry) populations. From among these 47 articles, we focused on 25 that provided quantitative data for genetic variants with significant association for some CVD outcome in one or both racial/ethnic groups (Web Table 1). The remaining 22 studies contained no relevant quantitative data or reported no significant association between a genetic variant and a cardiovascular outcome and were not considered further (Web Table 2). Following

colloquial usage, we refer to European ancestry populations interchangeably as "white" and African ancestry populations interchangeably as "black." Statistical analysis was conducted in Stata, version 12 (StataCorp LP, College Station, Texas) (32), and both Stata and the R language (version 3.0.2) (R Foundation for Statistical Computing, Vienna, Austria) (33) were used to create the figures.

RESULTS

Of the 47 relevant articles, only 3 included associations that were significant among both African and European ancestry populations, with only 3 SNPs meeting study-specific significance criteria (Table 1). The significant results were C825T in relation to hypertension, reported by Bagos et al. (34); rs10455872 for aortic valve calcification, reported by Thanassoulis et al. (35); and rs12425791 for stroke, reported by Ikram et al. (36). For C825T in relation to hypertension, the authors did not fit a race-stratified model but instead pooled the groups and reported a homogeneous association with an odds ratio of 1.17 (95% confidence interval: 1.06, 1.29). The risk allele, however, was more than twice as common in blacks (0.76 vs. 0.31), which suggests the potential to explain some observed racial disparity in hypertension in the general population. In the report by Thanassoulis et al., the association was almost twice as large in blacks (odds ratio = 3.57, 95% confidence interval: 1.42, 8.99) than in whites (odds ratio = 2.05, 95% confidence interval: 1.66, 2.53), but the risk allele was more than 3 times more common in whites (0.07 versus 0.02). Therefore, the variant, if causal, would actually contribute more excess cases to whites (37). Finally, the rs12425791 SNP reported by Ikram et al. had a roughly homogeneous hazard ratio for both groups in relation to total stroke and ischemic stroke and a nearly 2-fold higher prevalence of the risk allele in the white population (0.19 versus 0.10). Even if this association were causal, therefore, it could not contribute to an explanation for any observed disparity because it predicts a higher stroke burden in whites.

Of the 47 retrieved studies determined to be relevant, 6 (3–5, 7, 16, 19) reported on significant associations among only African ancestry populations in studies that included both African and European ancestry samples (Web Table 3). Of these, 12 associations across 13 variants were declared to be significant for 1 or more of a variety of CVD outcomes in blacks only, including hypertension, left ventricular hypertrophy, ischemic stroke, venous thromboembolism, and heart failure. In contrast, 14 retrieved papers (2, 3, 6, 7, 9–11, 14, 15, 17, 19, 20, 23, 25) reported significant associations among only European ancestry populations in studies that included both ancestry samples (Web Table 4). From these 14 reports, 22 variants were declared to be significantly associated with 1 or more of a variety of CVD outcomes in whites only. There were additionally 2 studies (12, 13) retrieved that reported 2 variants significantly associated with CVD outcomes in studies that included only African ancestry samples (Web Table 5). Finally, 6 retrieved studies (3, 8, 18, 21, 22, 24) reported 78 variants significantly associated with CVD outcomes in studies that included only European ancestry samples (Web Table 6).

For most outcomes, there were too few estimates for a quantitative summarization. In the case of ischemic stroke, however, we found 6 significant associations for blacks in 2 papers (36, 38) and 5 significant associations for whites in 3 papers (36, 38, 39), which allowed us to conduct a random-effects summarization to test statistically for racial group as a significant explanation for heterogeneous effects (Figure 2). Only one of these variants (rs12425791) was significantly associated with the outcome in both populations. The between-estimate variability as measured using the I^2 statistic calculated across the 11 reported associations was large (86%), but this

Table 1. Variants Associated With Cardiovascular Disease in Both African- and European-Ancestry Populations From Analyses That Included Both Groups (3 Variants From 3 Studies)

SNP	Gene	Group	Outcome	Effect	No. of Subjects	Allele Frequency	Allele	Effect Estimate		95% CI	Reference No.
								HR	OR		
C825T	*GNB3*	AA	Hypertension	Risk	1,332	0.76 cases; 0.76 controls	T		1.17	1.06, 1.29[a]	34
C825T	*GNB3*	EA	Hypertension	Risk	16,827	0.33 cases; 0.31 controls	T		1.17	1.06, 1.29[a]	34
rs10455872	*LPA*	AA	Aortic-valve calcification	Risk	2,496	0.02	G		3.57	1.42, 8.99	35
rs10455872	*LPA*	EA	Aortic-valve calcification	Risk	39,338	0.07	G		2.05	1.66, 2.53	35
rs10455872	*LPA*	EA	Aortic stenosis	Risk	308	0.07	G	1.68		1.32, 2.15	35
rs12425791	near *NINJ2*	AA	Total stroke	Risk	2,430	0.10	A	1.35		1.01, 1.79	36
rs12425791	near *NINJ2*	AA	Ischemic stroke	Risk	2,430	0.10	A	1.42		1.06, 1.91	36
rs12425791	near *NINJ2*	EA	Total stroke	Risk	19,602	0.19	A	1.30		1.19, 1.42	36
rs12425791	near *NINJ2*	EA	Ischemic stroke	Risk	19,602	0.19	A	1.33		1.21, 1.47	36

Abbreviations: AA, African ancestry; CI, confidence interval; EA, European ancestry; HR, hazard ratio; OR, odds ratio; SNP, single nucleotide polymorphism.

[a] This effect estimate was derived from the cohort of EA and AA subjects collectively; data were not separated by racial/ethnic group.

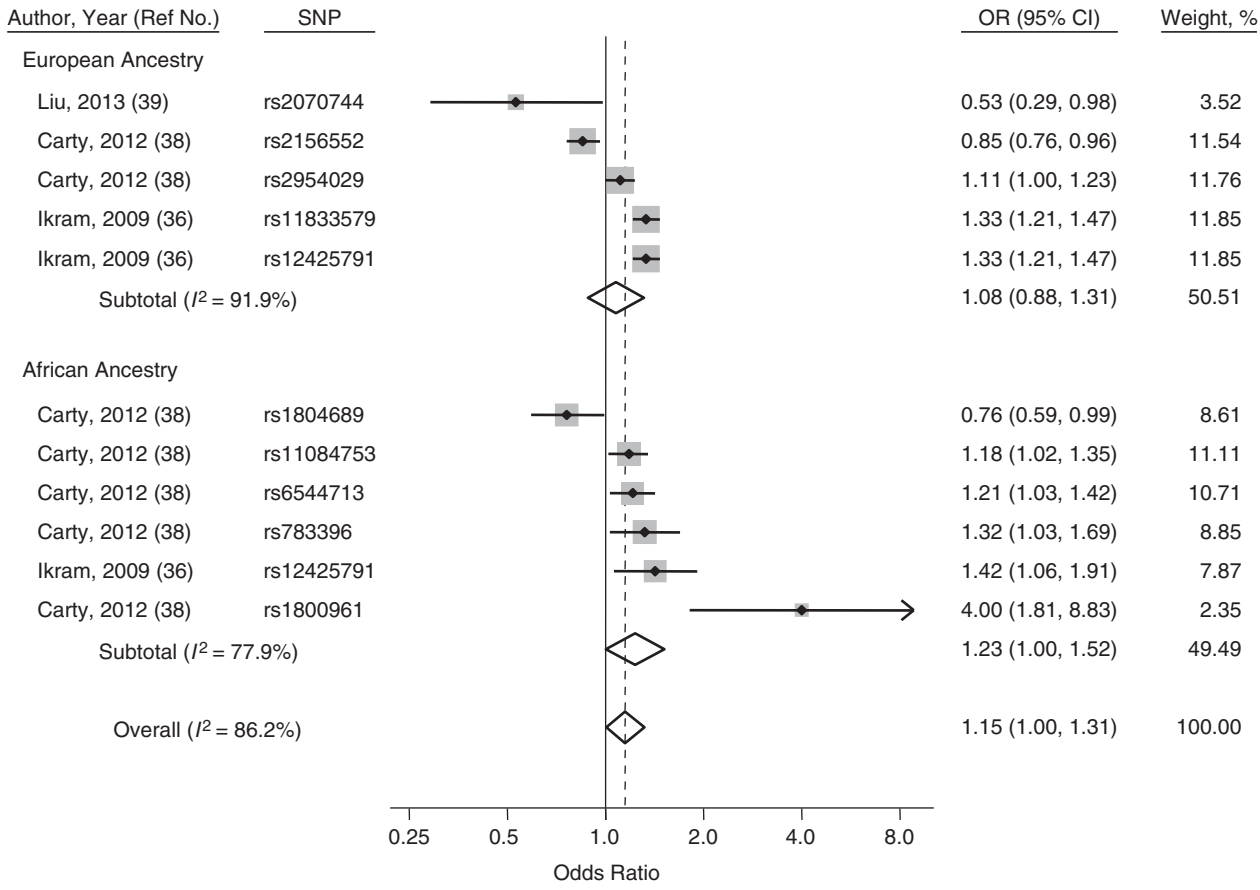

Figure 2. Forest plot of single nucleotide polymorphisms (SNPs) associated with ischemic stroke in African- and European-ancestry groups. Weights are from random-effects meta-analysis. CI, confidence interval; OR, odds ratio.

is not surprising because different variants should have different magnitudes of association with ischemic stroke. However, a meta-regression to explore whether racial/ethnic population is an explanatory factor for this effect heterogeneity showed that this factor fails to account for a significant portion of the between-estimate variation ($P = 0.4$). Therefore, there is little evidence from these data that the average effect size for discovered genetic risk factors for ischemic stroke in blacks differs in any way from that in whites (Web Appendix 3).

DISCUSSION

Despite the rapid increase in the number of genomic studies over the past decade that covered many outcomes, the accumulated evidence for a genetic contribution to CVD disparities in blacks versus whites has been essentially nil. There are several potential explanations for this surprising absence of evidence. The widely recognized problem of missing heritability in all association studies must be given first consideration (16). Even within populations, association studies have thus far explained only miniscule portions of observed phenotypic variation. For example, the cumulative evidence from GWAS of blood pressure explains less than 1% of variability in that trait (40). Secondly, only a small fraction of GWAS include populations of African ancestry, and the systematically smaller number of black participants yields substantially less power to detect associations. A strong correlation exists between the size of a GWAS discovery cohort and the number of associated variants discovered, with the number of discovered variants roughly doubling when the sample size is doubled (18). Our review demonstrates a consistently larger sample size for cohorts with European ancestry relative to cohorts with African ancestry across the included studies (Figure 3), which might contribute to the trend in the number of reported associations (Web Figure 1). In a recent review, Adeyemo and Rotimi (41) reported that only 7% of GWAS publications overall used African-ancestry groups for discovery cohorts, whereas the vast majority (69%) used European-ancestry groups. The bulk of SNP associations will therefore be discovered in European-ancestry groups.

Elements of study design might also contribute to the absence of reported genetic explanations for cardiovascular disparities. The SNP array technologies used in GWAS rely on linkage disequilibrium between a limited set of measured variants and other unmeasured variants across the genome.

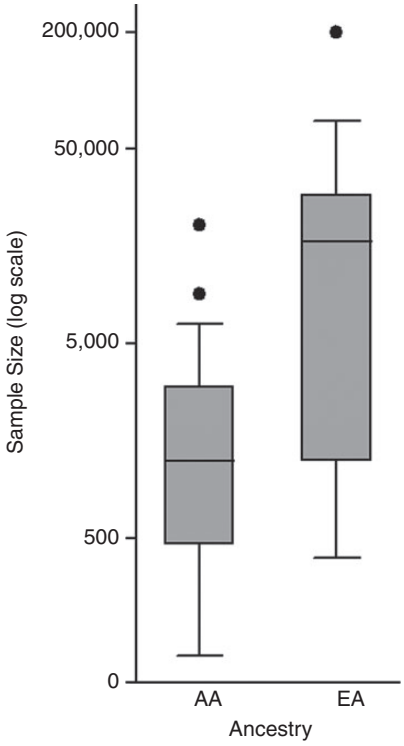

Figure 3. Boxplot of cohort sample sizes in studies with quantitative data ($n = 25$), stratified by racial/ethnic group.

Populations of African ancestry exhibit less linkage disequilibrium among loci, smaller haplotype blocks, and greater overall genetic diversity relative to other groups (42). These differences in haplotype structure allow for the possibility that standard SNP arrays provide inadequate coverage of the genome for black populations, potentially resulting in reduced power for detecting SNPs of etiologic relevance (43). Overcoming this limitation would require larger African-ancestry sample sizes, which may dissuade researchers from including these populations (44). Additionally, the SNPs present on the chips are common (e.g., minor allele frequency ≥5%) and are underpowered to detect rare variants because linkage disequilibrium decreases as a function of allele frequency difference. The result is a technology designed to detect associations between measured and unmeasured variants that are both common in the population (18). With a much greater degree of genetic diversity relative to other continental groups, however, African-ancestry populations have a higher frequency of rare variants; in 1 study, Guthery et al. (45) reported that as many as 64% of SNPs were rare across African-American genomes. This suggests that associations with (rare) causal variants in African-ancestry populations might be differentially missed (Web Figures 2, 3A, and 3B).

In a recent systematic review of cancer outcomes, Jing et al. (46) reported results largely consistent with our findings for CVD, namely an absence of evidence for heterogeneity of effects across groups and a general failure of associations identified in one group to replicate in another. In contrast, however, some authors have reported more substantial heterogeneity across ancestry groups. For example, in a comparison of SNP associations of genome-wide significance across multiple studies, a difference of more than 10% in absolute frequency of the minor allele was reported in approximately 70% of European-ancestry versus African-ancestry comparisons (47). More than 20% of these estimates were in opposite directions, 58% shared direction but had a greater than 2-fold difference, and 42% differed "beyond chance." However, of the 108 "robustly replicated associations" reviewed in that study, only 1 concerned a cardiovascular outcome for which data were available from an African-ancestry sample. This result was found for rs12425791 (near Ninjurin 2 (*NINJ2*)), which confers greater risk for whites (36). Similarly, it has been reported that more than 25% of tagging SNP associations identified in European-ancestry groups have significantly different effect sizes in 1 or more non-European ethnic groups (48). Conversely, in a meta-analysis of candidate gene studies that focused on CVD, estimates differed importantly between racial/ethnic groups in only 14% of cases, suggesting mostly common biological effects for variants discovered through this more specific methodology (49). These authors concluded that "any estimate of genetic contribution to the disparity in incidence of disease between 2 populations at this stage seems to be an elusive goal . . . . [S]tatements about specific variants or clusters thereof explaining the difference in disease incidence and prevalence in different populations and thus having clinical or public health consequences are precarious" (50, p. 836).

Given the disappointing yield from GWAS, there have been many recent suggestions in the literature that gene-environment interactions and epigenetics will become increasingly important for understanding racial disparities in CVD. For example, Kuzawa and Sweet (51) reviewed evidence of developmental origins of adult disease and proposed a mechanism through which racial disparities in birth weight could be manifested in adult chronic disease distributions. They described animal studies and other indirect evidence to establish the plausibility of this mechanism in principle, but even 5 years after their article was published, direct evidence of such epigenetic mechanisms in humans remains infrequent and inconsistent. The GWAS era may eventually yield to a subsequent era in which the focus is on environmental modification of gene expression, but in the 7-year period of our study, such work remained largely speculative and tenuous.

A genetic explanation for an observed disparity logically requires that a causal variant have an effect on risk and either a different prevalence across the populations or a different magnitude of effect. However, verifying these conditions is hindered by the inherent limitations in reported genetic association data. Whereas association studies reveal correlations between case status and a specific SNP, the identified polymorphism is rarely the causal variant itself (52). The most parsimonious inference is that nearby genes are likely to harbor the causal variant, but the mechanism underlying the association usually remains obscure, especially when the significant SNP is not in the proximity of any known genes (53). When the association is not causal, the prevalence of the risk allele might be less relevant for observed disparities.

Most associations discovered in our search appeared to be specific to one racial/ethnic group or the other. It is tempting to think that a mutation that appears to confer susceptibility in only one group might help explain why that group has a higher observed incidence of disease. Unfortunately, there is no unambiguous interpretation of relative risk information from case-control designs with respect to observed disparities. For example, suppose that at a certain locus in blacks can be TT (81%), TC (18%), or CC (1%), with risks of 1 in 100 for TT and 2 in 100 for TC/CC, such that relative risk among blacks is 2.0. Further suppose that for whites there is no association, so that the relative risk is 1.0 (TC/CC vs. TT). Does this variant therefore contribute to excess attributable cases for blacks? These data do not provide enough information to answer this question. If the homogeneous risk in whites is 2 or more in 100, then this variant cannot be said to explain any excess risk in blacks, even though the relative risk is 2.0. Rather, it would imply that 81% of blacks are protected in a way that whites are not. Therefore, without the baseline risk information, the genetic association in only one group cannot be interpreted meaningfully with respect to any observed disparity. This constitutes a severe limitation of ratio-based approaches for reporting the effects of genetic differences at the population level.

We focused our search on reviews and meta-analyses in order to identify stable associations that are well replicated. Nonetheless, even among the tiny number of reported SNPs that were investigated in both groups, there is some doubt as to their long-term viability as active functional hypotheses. For example, corin serine peptidase (*CORIN*) gene variants were associated with hypertension (54) and left-ventricular hypertrophy (55) among African Americans in 2 different study populations and yet were almost completely unobserved in populations of European ancestry. Nonetheless, these variants have not been reported to be associated with any cardiovascular outcome in any population in any studies over the subsequent 7 years, including those with larger African-ancestry samples. Although there is no published null finding, the absence of any subsequent corroborations or replications does not bode well for any developing consensus around this explanatory hypothesis.

On the other hand, we note that our search strategy failed to select 1 large GWAS with data on European and African ancestry populations. The International Consortium for Blood Pressure GWAS (40) included more than 203,000 subjects of European ancestry and 19,775 subjects of African ancestry, but it was not captured by our search because it was classified neither as a meta-analysis nor as a review and because the associations for the African-ancestry populations were reported only in the appendices. A number of selected studies (e.g., Bhatnagar et al. (56)) summarized some of the International Consortium for Blood Pressure findings, but they tended to only mention the data from European cohorts that were presented as main analyses. Review of the supplementary material from the International Consortium for Blood Pressure study revealed that some of the reported SNPs were in fact associated in both European and African ancestry populations. Nonetheless, we followed the prespecified study protocol and did not include this replication data. This means that there are a few additional associations that we report as found in Europeans only (Web Table 6) but that were also associated in the African-ancestry sample in the International Consortium for Blood Pressure appendices.

The fact that our results show so little stable evidence of genetic explanations for racial disparities in CVD could be attributed to a general failure of GWAS to explain observed disease phenotypes (18). Inconsistencies across studies of genetic associations are a long-standing and vexing problem in all contexts, not just with respect to racial disparities (57). Certainly there are limitations peculiar to a stratification variable as ambiguous and heterogeneous as "race" (58), on top of the more general methodological limitations that arise from unrepresentative samples, publication bias, false positives, modification by contrasting environments, and a host of other difficulties that are beyond the scope of the present article. Nonetheless, there do exist dramatic success stories for other outcomes. For example, chronic kidney disease accounts for 3–4 months of lost life expectancy or 5%–8% of the total racial disparity in life expectancy (22). African Americans have roughly 4-times the lifetime risk of end-stage renal disease as whites, and GWAS have successfully identified variants of the apolipoprotein L, 1 (*APOL1*) gene as important risk alleles (59). Jointly occurring G1 and G2 variants of *APOL1* had odds ratios for 10- to 30-fold associations with various chronic kidney pathologies, an order of magnitude higher than anything reported for CVD. Moreover, the prevalences of these variants are markedly distinct between West Africans and Europeans, and it has since been posited that these represent adaptive mutations against trypanosomiasis (60). Prevalence and association estimates reported in the current literature suggest that up to half of excess incident cases of nondiabetic kidney disease in US blacks are due to these mutations, accounting for approximately 1%–2% of excess mortality in blacks (61). These estimates are small in absolute terms but show the potential for GWAS to reveal important causal explanations for disparities when they exist. The absence of any similar discovery for common CVDs, which confer a much greater population burden of morbidity and mortality, is not encouraging for a potential genetic explanation, at least not one involving relatively common SNPs.

In summary, we conducted a systematic search for review articles and meta-analyses that described results from genomic studies of CVD in which data from populations of European and African ancestry were available. The results reveal a striking absence of evidence to support the assertion that any important component of observed disparities in these diseases arises from main effect genetic mechanisms as we currently understand them. Only a handful of associations are present in both populations, and these associations are small in magnitude, have generally not been widely replicated in other samples, and are arrayed in no consistent direction that might favor one racial/ethnic group over the other. Despite the enormous social investment in genomic studies, this research program has not yet provided valuable population-relevant insights into disparities in the most common cause of morbidity and mortality. Progress in eliminating disparities is described as a primary policy objective by government agencies and was promised as one of the key products of the GWAS era (62), yet it clearly requires either a new approach

to genetic factors or a shift in resources to research on other explanatory mechanisms (63).

ACKNOWLEDGMENTS

Author affiliations: Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, Quebec, Canada (Jay S. Kaufman, Dinela Rushani); Department of Human Genetics, McGill University, Montreal, Quebec, Canada (Lena Dolman); and Department of Public Health Sciences, Stritch School of Medicine, Loyola University, Maywood, Illinois (Richard S. Cooper).

This work was supported by the Canada Research Chairs program.

Conflict of interest: none declared.

REFERENCES

1. Polednak AP. *Racial & Ethnic Differences in Disease*. Oxford, UK: Oxford University Press; 1989.
2. Budrys G. *Unequal Health: How Inequality Contributes to Health or Illness*. Oxford, UK: Rowman and Littlefield Publishers; 2003.
3. Sarich V, Miele F. *Race: The Reality of Human Differences*. Oxford, UK: Westview Press; 2009.
4. Piel FB, Patil AP, Howes RE, et al. Global distribution of the sickle cell gene and geographical confirmation of the malaria hypothesis. *Nat Commun*. 2010;1:104.
5. Lee C. "Race" and "ethnicity" in biomedical research: do scientists construct and explain differences in health? *Soc Sci Med*. 2009;68(6):1183–1190.
6. Morning A. *The Nature of Race: How Scientists Think and Teach About Human Difference*. Berkeley and Los Angeles, CA: University of California Press; 2011.
7. Williams DR. Race and health: basic questions, emerging directions. *Ann Epidemiol*. 1997;7(5):322–333.
8. Risch N, Burchard E, Ziv E, et al. Categorization of humans in biomedical research: genes, race and disease. *Genome Biol*. 2002;3(7):comment2007.1-2007.12.
9. Frank R. What to make of it? The (Re)emergence of a biological conceptualization of race in health disparities research. *Soc Sci Med*. 2007;64(10):1977–1983.
10. Kaufman JS, Cooper RS. Race in epidemiology: new tools, old problems. *Ann Epidemiol*. 2008;18(2):119–123.
11. Cooper RS, Kaufman JS. Race and hypertension: science and nescience. *Hypertension*. 1998;32(5):813–816.
12. Kaufman JS, Cooper RS, McGee DL. Socioeconomic status and health in blacks and whites: the problem of residual confounding and the resiliency of race. *Epidemiology*. 1997;8(6):621–628.
13. Maher B. Personal genomes: the case of the missing heritability. *Nature*. 2008;456(7218):18–21.
14. Moore D. *The Dependent Gene: The Fallacy of "Nature vs. Nurture"*. New York, NY: Holt Paperbacks; 2003.
15. Robinson-Cohen C, Hoofnagle AN, Ix JH, et al. Racial differences in the association of serum 25-hydroxyvitamin D concentration with coronary heart disease events. *JAMA*. 2013;310(2):179–188.
16. Zuk O, Hechter E, Sunyaev SR, et al. The mystery of missing heritability: genetic interactions create phantom heritability. *Proc Natl Acad Sci U S A*. 2012;109(4):1193–1198.
17. Stenberg A. Interpreting estimates of heritability—a note on the twin decomposition. *Econ Hum Biol*. 2013;11(2):201–205.
18. Visscher PM, Brown MA, McCarthy MI, et al. Five years of GWAS discovery. *Am J Hum Genet*. 2012;90(1):7–24.
19. Hindorff LA, MacArthur J, Morales J, et al. A catalog of published genome-wide association studies. http://www.genome.gov/gwastudies. Updated October 6, 2014. Accessed April 20, 2014.
20. Pohlhaus JR, Cook-Deegan RM. Genomics research: world survey of public funding. *BMC Genomics*. 2008;9:472.
21. Feero WG, Guttmacher AE, Collins FS. Genomic medicine—an updated primer. *N Engl J Med*. 2010;362(21):2001–2011.
22. Harper S, Rushani D, Kaufman JS. Trends in the black-white life expectancy gap, 2003–2008. *JAMA*. 2012;307(21):2257–2259.
23. Gillespie CD, Wigington C, Hong Y; Centers for Disease Control and Prevention (CDC). Supplement: CDC health disparities and inequalities report—United States, 2013. *MMWR Surveill Summ*. 2013;62(Suppl 3):157–160.
24. Sharma A, Colvin-Adams M, Yancy CW. Heart failure in African Americans: disparities can be overcome. *Cleve Clin J Med*. 2014;81(5):301–311.
25. White RH, Keenan CR. Effects of race and ethnicity on the incidence of venous thromboembolism. *Thromb Res*. 2009;123(Suppl 4):S11–S17.
26. Zakai NA, McClure LA. Racial differences in venous thromboembolism. *J Thromb Haemost*. 2011;9(10):1877–1882.
27. Ferdinand KC, Armani AM. The management of hypertension in African Americans. *Crit Pathw Cardiol*. 2007;6(2):67–71.
28. Burt VL, Cutler JA, Higgins M, et al. Trends in the prevalence, awareness, treatment, and control of hypertension in the adult US population. Data from the health examination surveys, 1960 to 1991. *Hypertension*. 1995;26(1):60–69.
29. Rosamond W, Flegal K, Furie K, et al. Heart disease and stroke statistics–2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation*. 2008;117(4):e25–e146.
30. Redmond N, Baer HJ, Hicks LS. Health behaviors and racial disparity in blood pressure control in the national health and nutrition examination survey. *Hypertension*. 2011;57(3):383–389.
31. Pruissen DM, Kappelle LJ, Rosendaal FR, et al. Genetic association studies in ischaemic stroke: replication failure and prospects. *Cerebrovasc Dis*. 2009;27(3):290–294.
32. Stata Corporation. Stata statistical software, release 12. College Station, TX: Stata Corporation; 2011.
33. R Core Team. *R: a Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing; 2013.
34. Bagos PG, Elefsinioti AL, Nikolopoulos GK, et al. The GNB3 C825T polymorphism and essential hypertension: a meta-analysis of 34 studies including 14,094 cases and 17,760 controls. *J Hypertens*. 2007;25(3):487–500.
35. Thanassoulis G, Campbell CY, Owens DS, et al. Genetic associations with valvular calcification and aortic stenosis. *N Engl J Med*. 2013;368(6):503–512.
36. Ikram MA, Seshadri S, Bis JC, et al. Genomewide association studies of stroke. *N Engl J Med*. 2009;360(17):1718–1728.
37. Rockhill B, Newman B, Weinberg C. Use and misuse of population attributable fractions. *Am J Public Health*. 1998;88(1):15–19.

38. Carty CL, Buzková P, Fornage M, et al. Associations between incident ischemic stroke events and stroke and cardiovascular disease-related genome-wide association studies single nucleotide polymorphisms in the Population Architecture Using Genomics and Epidemiology study. *Circ Cardiovasc Genet*. 2012;5(2):210–216.
39. Liu R, Geng P, Ma M, et al. Association between endothelial nitric oxide synthase gene polymorphism (T-786C) and ischemic stroke susceptibility: a meta-analysis. *Int J Neurosci*. 2014;124(9):642–651.
40. International Consortium for Blood Pressure Genome-Wide Association Studies. Genetic variants in novel pathways influence blood pressure and cardiovascular disease risk. *Nature*. 2011;478(7367):103–109.
41. Adeyemo A, Rotimi C. What does genomic medicine mean for diverse populations? *Mol Genet Genomic Med*. 2014; 2(1):3–6.
42. Campbell MC, Tishkoff SA. African genetic diversity: implications for human demographic history, modern human origins, and complex disease mapping. *Annu Rev Genomics Hum Genet*. 2008;9:403–433.
43. Wojczynski MK, Li M, Bielak LF, et al. Genetics of coronary artery calcification among African Americans, a meta-analysis. *BMC Med Genet*. 2013;14:75.
44. Need AC, Goldstein DB. Next generation disparities in human genomics: concerns and remedies. *Trends Genet*. 2009;25(11): 489–494.
45. Guthery SL, Salisbury BA, Pungliya MS, et al. The structure of common genetic variation in United States populations. *Am J Hum Genet*. 2007;81(6):1221–1231.
46. Jing L, Su L, Ring BZ. Ethnic background and genetic variation in the evaluation of cancer risk: a systematic review. *PLoS One*. 2014;9(6):e97522.
47. Ntzani EE, Liberopoulos G, Manolio TA, et al. Consistency of genome-wide associations across major ancestral groups. *Hum Genet*. 2012;131(7):1057–1071.
48. Carlson CS, Matise TC, North KE, et al. Generalization and dilution of association results from European GWAS in populations of non-European ancestry: the PAGE . *PLoS Biol*. 2013;11(9):e1001661.
49. Ioannidis JP, Ntzani EE, Trikalinos TA. 'Racial' differences in genetic effects for complex diseases. *Nat Genet*. 2004;36(12): 1312–1318.
50. Moonesinghe R, Ioannidis JP, Flanders WD, et al. Estimating the contribution of genetic variants to difference in incidence of disease between population groups. *Eur J Hum Genet*. 2012; 20(8):831–836.
51. Kuzawa CW, Sweet E. Epigenetics and the embodiment of race: developmental origins of US racial disparities in cardiovascular health. *Am J Hum Biol*. 2009;21(1):2–15.
52. Wang K, Dickson SP, Stolle CA, et al. Interpretation of association signals and identification of causal variants from genome-wide association studies. *Am J Hum Genet*. 2010; 86(5):730–742.
53. McClellan J, King MC. Genetic heterogeneity in human disease. *Cell*. 2010;141(2):210–217.
54. Dries DL, Victor RG, Rame JE, et al. Corin gene minor allele defined by 2 missense mutations is common in blacks and associated with high blood pressure and hypertension. *Circulation*. 2005;112(16):2403–2410.
55. Rame JE, Drazner MH, Post W, et al. Corin I555(P568) allele is associated with enhanced cardiac hypertrophic response to increased systemic afterload. *Hypertension*. 2007;49(4): 857–864.
56. Bhatnagar P, Barron-Casella E, Bean CJ, et al. Genome-wide meta-analysis of systolic blood pressure in children with sickle cell disease. *PLoS One*. 2013;8(9):e74193.
57. Ioannidis JP. Non-replication and inconsistency in the genome-wide association setting. *Hum Hered*. 2007;64(4): 203–213.
58. Kaplan JB. The Quality of Data on "Race" and "Ethnicity": implications for health researchers, policy makers, and practitioners. *Race Soc Probl*. 2014;6(3):214–236.
59. Genovese G, Friedman DJ, Ross MD, et al. Association of trypanolytic ApoL1 variants with kidney disease in African Americans. *Science*. 2010;329(5993):841–845.
60. Rosset S, Tzur S, Behar DM, et al. The population genetics of chronic kidney disease: insights from the MYH9-APOL1 locus. *Nat Rev Nephrol*. 2011;7(6):313–326.
61. Kaufman JS, Rushani D, Cooper RS. Nature versus nurture in the explanations for racial/ethnic health disparities: parsing disparities in the era of genome-wide association studies. In: Suzuki K, von Vacano D, eds. *Reconsidering Race: Global and Comparative Studies in Race and Genomics*. London, UK: Oxford University Press. In press.
62. Collins FS, Green ED, Guttmacher AE, et al.; US National Human Genome Research Institute. A vision for the future of genomics research. *Nature*. 2003;422(6934):835–847.
63. Diez Roux AV. Conceptual approaches to the study of health disparities. *Annu Rev Public Health*. 2012;33:41–58.
64. Gohil R, Peck G, Sharma P. The genetics of venous thromboembolism. A meta-analysis involving approximately 120,000 cases and 180,000 controls. *Thromb Haemost*. 2009; 102(2):360–370.