BACKGROUND: Genetic variation at chromosome 9p21 is a recognized risk factor for coronary heart disease (CHD). However, its effect on disease progression and subsequent events is unclear, raising questions about its value for stratification of residual risk.

METHODS: A variant at chromosome 9p21 (rs1333049) was tested for association with subsequent events during follow-up in 103,357 Europeans with established CHD at baseline from the GENIUS-CHD (Genetics of Subsequent Coronary Heart Disease) Consortium (73.1% male, mean age 62.9 years). The primary outcome, subsequent CHD death or myocardial infarction (CHD death/myocardial infarction), occurred in 13,040 of the 93,115 participants with available outcome data. Effect estimates were compared with case/control risk obtained from the CARDIoGRAMplusC4D consortium (Coronary Artery Disease Genome-wide Replication and Meta-analysis [CARDIoGRAM] plus The Coronary Artery Disease [C4D] Genetics) including 47,222 CHD cases and 122,264 controls free of CHD.

RESULTS: Meta-analyses revealed no significant association between chromosome 9p21 and the primary outcome of CHD death/myocardial infarction among those with established CHD at baseline (GENIUS-CHD odds ratio, 1.02; 95% CI, 0.99–1.05). This contrasted with a strong association in CARDIoGRAMplusC4D odds ratio 1.20; 95% CI, 1.18–1.22; P for interaction <0.001 compared with the GENIUS-CHD estimate. Similarly, no clear associations were identified for additional subsequent outcomes, including all-cause death, although we found a modest positive association between chromosome 9p21 and subsequent revascularization (odds ratio, 1.07; 95% CI, 1.04–1.09).

CONCLUSIONS: In contrast to studies comparing individuals with CHD to disease-free controls, we found no clear association between genetic variation at chromosome 9p21 and risk of subsequent acute CHD events when all individuals had CHD at baseline. However, the association with subsequent revascularization may support the postulated mechanism of chromosome 9p21 for promoting atheroma development.
Using a case-control approach, a large number of common genetic variants have now been associated with coronary heart disease (CHD) through genome-wide association studies, in an effort largely led by the CARDIoGRAMPlusC4D consortium (Coronary Artery Disease Genome-wide Replication and Meta-analysis [CARDIoGRAM] plus The Coronary Artery Disease [C4D] Genetics). Among these variants, the chromosome 9p21 locus was the first to be discovered and the variant with the largest individual effect and is the most widely replicated genetic risk factor for CHD. Multiple studies including case-control and prospective cohort studies in general populations have reliably confirmed its effect on risk of CHD among otherwise healthy individuals.

However, it is uncertain whether variants at the 9p21 locus also affect risk of recurrent or subsequent events, including mortality in those with established CHD. Elucidation of this hypothesis would help to better understand its mechanism and estimate its incremental value for stratification of residual risk. Prior studies have shown conflicting results, although most have been underpowered. A literature-based meta-analysis indicated a null association of chromosome 9p21 variants with subsequent CHD events but was based on summary, not individual level data, with varying outcome definitions.

The new collaborative GENIUS-CHD (Genetics of Subsequent Coronary Heart Disease) consortium, described in this issue of the journal, was established to investigate genetic determinants of disease progression following an index CHD event.

In this article, we use the GENIUS-CHD resource to: (1) examine the association of variants at the 9p21 locus on risk of subsequent CHD events in individuals with established CHD; (2) compare these to the association between chromosome 9p21 and any CHD observed in the CARDIoGRAMPlusC4D consortium; and (3) explore the potential impact on these estimates of biases that might affect genetic association studies of disease outcome and prognosis.

**METHODS**

In accordance with Transparency and Openness Promotion Guidelines, the data, analytic methods, and study materials will be made available to other researchers for purposes of reproducing the results or replicating the procedure. Participating studies received local institutional review board approval and included patients who had provided informed consent at the time of enrollment. The central analysis sites also received waivers from their local institutional review board for collating and analysing summary level data from these individual studies. Details about the GENIUS-CHD consortium and study inclusion criteria have been published separately in this issue of the journal, whereas for this study full details about data sources, genetic variant selection, outcomes and statistical analyses are available in the Data Supplement.

**RESULTS**

In total, 49 studies from the GENIUS-CHD consortium contributed to the federated analysis resulting in a sample size of 103,357 individuals of European descent with established CHD and available genotype data at the 9p21 locus. Of these, 93,115 individuals had available data for the primary composite outcome of subsequent CHD death/myocardial infarction (MI), of whom 13,040 experienced these events. Contributing study details are provided in Table. Participant characteristics are representative for populations with established CHD with a weighted mean age of 62.9 years; 73.1% male. As expected, risk factor prevalence was high in this population, including diabetes mellitus (24.4%), hypertension (59.1%), and current smoking (25.7%). Statin use at enrollment varied by study, ranging from 5.2% to 97.3%, with a median of 61.5% (Table).

The rs1333049 single nucleotide polymorphism was genotyped in 42 studies, with the remaining 7 studies using highly correlated proxies (R^2 > 0.90); rs10757278 (4 studies) or rs4977574 (3 studies) when the primary single nucleotide polymorphism was unavailable. Genotyping details are provided in Table I in the Data Supplement. For rs1333049, the average risk allele frequency across the participating studies was 0.518 ranging from 0.453 to 0.587 (Figure I in the Data Supplement).

From CARDIOGRAMplusC4D, after excluding 6 cohorts which had contributed data to both consortia, data were available for association with chromosome 9p21 from 41 studies, including 47,222 cases with CHD and 122,264 controls free of any CHD.

Power to detect different effect sizes, including the effect size identified in CARDIOGRAMplusC4D, using a 2-sided alpha of 0.05, are provided in Table II in the Data Supplement.

**Chromosome 9p21 Association With Subsequent CHD Events**

Study-specific results for the association between chromosome 9p21 and risk of the primary outcome of CHD death or MI among individuals with established CHD at baseline, adjusted for age and sex are presented in Figure II in the Data Supplement.

The per-allele odds ratio (OR) for the primary outcome during follow-up was 1.02 (95% CI, 0.99–1.05). The effect estimate again for the primary outcome, based on a time to event analysis and using a Cox regression model, was also similar with a hazard ratio of 1.02 (95% CI, 0.99–1.04; Figure III in the Data Supplement).

In contrast, a meta-analysis of CARDIOGRAMplusC4D data (excluding studies also contributing data to
Table. Overview of Studies Contributing to Chromosome 9p21 Analysis and Participant Characteristics

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Overview of studies contributing to chromosome 9p21 analysis and participant characteristics; alias denotes the abbreviated name of each study used in figures and tables; PubMed IDs are provided for individual study descriptions; mean (SD) with proportions (%) are provided unless otherwise stated. ACS indicates acute coronary syndrome; BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; FRISC-II, Fast Revascularization during Instability in Coronary artery disease; GENIUS-CHD, Genetics of Subsequent Coronary Heart Disease; JUMC, Jagiellonian University Medical College; KAROLA, Langzeitfolge der Kardiologischen Anschlussbehandlung; LIFE, The Leipzig Heart Study; MI, myocardial infarction; RCT, randomized controlled trial; and WTCCC, Wellcome Trust Case Control Consortium.
GENIUS-CHD), revealed a per-allele OR for a CHD event similar to that reported previously (OR, 1.20; 95% CI, 1.18–1.22). There was evidence of statistical heterogeneity between the estimates (interaction $P<0.001$), Figure 1.

**Subgroup Analyses**

We found minimal evidence for heterogeneity in effect estimates when stratifying by CHD subtype at baseline (interaction $P$ value 0.801), with no clear evidence for an effect of chromosome 9p21 genetic variation on subsequent CHD death or MI in individuals enrolled with acute coronary syndrome (OR, 1.02; 95% CI, 0.97–1.06), those with coronary artery disease with a prior MI (OR, 1.01; 95% CI, 0.96–1.05), and those with coronary artery disease without prior MI (OR, 1.01; 95% CI, 0.95–1.08, Figure 1).

We further examined the effect of chromosome 9p21 on the primary outcome in prespecified subgroup analyses. We noted a borderline nominally significant interaction with sex, suggesting a greater risk among women with the chromosome 9p21 risk allele, for subsequent CHD death/MI (interaction $P$ value = 0.04), whereas nonsignificant trends were noted for greater risk in those without hypertension ($P$ value=0.08) or without renal impairment ($P$ value=0.17). There were minimal differences in effect estimates by other patient level characteristics including age and diabetes mellitus or according to statin or antiplatelet use or left ventricular impairment at baseline (Figure IV in the Data Supplement).

Similarly, when stratified by study level features, we observed minimal evidence for heterogeneity in effect estimates by study size, geographic region, study design, or length of follow-up (Figure V in the Data Supplement).

For the CARDioGRAMPlusC4D consortium (Coronary Artery Disease Genome wide Replication and Meta-analysis [CARDioGRAM] plus The Coronary Artery Disease [C4D] Genetics) meta-analysis estimate, 6 studies (LURIC, LIFE-Heart [The Leipzig Heart Study], GoDARTS [Genetics of Diabetes Audit and Research in Tayside Scotland], OHGS [Ottawa Heart Genomics Study], PROSPER [Prospective Study of Pravastatin in the Elderly at Risk], WTCCC [Welcome Trust Case Control Consortium]) were excluded as they were also included in GENIUS-CHD. Estimates for GENIUS-CHD are also presented by subtype of CHD at baseline, including acute coronary syndrome (ACS), stable coronary artery disease (CAD) without prior myocardial infarction (MI; CAD/no MI), and stable CAD with prior MI (CAD/MI). All estimates were adjusted for age and sex.
tions from the 1000 Genomes (Phase 3),9 (0.472). This

tion in the UKB (0.481) and European reference popula-

tion.8 We found that (1) in contrast to the known
strong association with CHD observed in CARDIo-
GRAMPlusC4D, there was a markedly attenuated and
nonsignificant association with subsequent CHD events
in GENIUS-CHD; (2) effect estimates in GENIUS-CHD
were broadly consistent in stratified analyses based on
features related to study design, patient characteristics,
and type of index CHD event; and (3) exploratory
analyses suggested that selection biases were unlikely
to explain the discrepancy. However, we did find evi-
dence of an association between these variants and a
secondary outcome of future revascularization events.
Our findings, taken together with those from others,
support the view that chromosome 9p21 promotes
CHD through progressive stable atheroma rather than
through development of an unstable phenotype.

The chromosome 9p21 locus is the most widely repli-
cated genetic risk locus for CHD identified to date, with
an estimated 15% to 35% increased risk in carriers of
the variant allele in prospective population and case-
control studies.5 However, studies examining the effect
on subsequent CHD events in people with known CHD
at baseline have reported conflicting results.10-14 Our
group previously examined this in a literature-based
meta-analysis, based on 15 studies with median sample
size of 1750 individuals, accruing 25 163 cases of estab-
lished CHD, and reported no clear evidence of an effect
of variants at chromosome 9p21 on the risk of subse-
quent events.6 An analysis by the CHARGE consortium
(The Cohorts for Heart and Aging Research in Genomic
Epidemiology) of 2953 MI survivors also reported no
association with subsequent mortality.7 However, the
limited size of most prior studies and the limitations
of literature meta-analyses indicate that many possible
explanations, including errors in risk allele coding and
selection biases, could not be adequately explored,
precluding meaningful interpretations for any mechanistic
or clinical implications.

The emergence of the GENIUS-CHD Consortium has
now permitted a robust evaluation of the role of chro-
mosome 9p21 in subsequent CHD event risk, revealing
a clear lack of association with a common compos-
ite coronary end point. This is in marked contrast to
findings from studies comparing cases to CHD-free
controls, as confirmed through meta-analysis of CAR-
DloGRAMPlusC4D data. Furthermore, we were able to

DISCUSSION

In this study, we examined the effect of genetic varia-
tion at the chromosome 9p21 locus on risk of subse-
quent events in 103 357 individuals with established
CHD using the newly formed GENIUS-CHD consor-
tium.8 We found that (1) in contrast to the known

Secondary Outcomes

We additionally examined the association between chro-
mosome 9p21 and other subsequent events available for
this analysis within the GENIUS-CHD Consortium, listed in
Table III in the Data Supplement, with summary estimates
provided in Figure 2. Of note, the per-allele effect of risk
variants at chromosome 9p21 on subsequent revascular-
ization during follow-up was 1.07 (95% CI, 1.04–1.09).
The effect on the composite outcome of any cardiovas-
cular disease, which includes revascularization, was also
significant at 1.04 (95% CI, 1.02–1.07). However, there
was no clear evidence of association for the remaining
secondary outcomes, with only a marginal trend to pro-
tection for both subsequent heart failure (OR, 0.97; 95%,
CI 0.93–1.01) and cardiovascular disease death (OR, 0.97;
95% CI, 0.94–1.01), as shown in Figure 2.

Selection Bias

To explore the potential for index event bias, we
looked for differences in associations between chro-
mosome 9p21 and known cardiovascular risk factors
in the United Kingdom Biobank, among the subset
of participants with established CHD, compared with
the full UKB cohort (Table IV in the Data Supplement).
Although there were differences between the groups
in the prevalence or values of the tested risk factors,
we did not find clear evidence to indicate a distortion
in associations between chromosome 9p21 and age,
blood pressure, diabetes mellitus, or smoking. There
was, however, a small difference for body mass index,
with a greater statistical association between the chro-
mosome 9p21 risk allele and lower body mass index
identified in those with established CHD than in the
general population (nominal interaction P value 0.02,
Table IV in the Data Supplement).

We also observed that the chromosome 9p21 risk
allele frequency in those surviving with CHD, both in
UKB (0.529) and in GENIUS-CHD (0.518, Figure I in the
Data Supplement), was higher than the general popula-
tion in the UKB (0.481) and European reference populat-
ions from the 1000 Genomes (Phase 3),9 (0.472). This
difference in frequency confirms the association of chro-
mosome 9p21 with CHD and also indicated absence of a
crude survival bias with loss of large numbers of
risk allele carriers to fatal events before entry into CHD
cohorts. We did, however, observe a trend to an age
association in those with established CHD, as well as the
general population in the UKB, with lower chromosome
9p21 risk allele frequencies with advancing age, relative
to younger carriers (Figure VI in the Data Supplement).
add to previous findings by showing that the type of CHD at baseline, whether acute coronary syndrome or stable CHD with or without prior MI, does not alter this association. We also interrogated several widely proposed explanations that could account for our findings through prespecified subgroup analyses and confirmed that most of these, specifically older age, medication use at baseline (statin or antiplatelet), study size or follow-up duration, did not appreciably alter the association findings. Our finding of a possible interaction with sex, warrants further investigation but should be considered hypothesis-generating given the borderline evidence of an interaction.

Selection bias (ie, index event bias or collider-stratification bias) could potentially explain reversed or attenuated associations in disease progression studies like this, operating by inducing relationships between (otherwise independent) risk factors through the selection of individuals with disease. Specifically, individuals surviving a first event consequent on exposure to a particularly strong risk factor may have lower levels of exposure to other individually weaker, independent risk factors, which can then attenuate the association of the risk factor of interest with subsequent events. However, the distribution of common risk factors by chromosome 9p21 genotype did not differ when compared between the general population and the subset with CHD in the UKB, using interaction tests. The only exception was for body mass index, a potentially differential association with chromosome 9p21 in those with CHD compared with the general population was noted. However, the effect size was small in both populations and on its own is unlikely to indicate presence of substantial index event bias.

Selection bias may also theoretically occur by focusing on subjects surviving a first event, where chromosome 9p21 risk allele carriers at risk of fatal CHD events are lost before enrollment into CHD cohorts, thereby diluting the future impact of the variant on subsequent CHD events. In this scenario, we would expect a lower risk allele frequency in those surviving CHD and entering CHD cohorts, but we found no evidence for this. Among those with CHD in the UKB, and among the whole UKB cohort, we did find a progressive loss of risk allele carriers with increasing age, consistent with prior findings of a greater association with CHD, among younger individuals in case-control studies. Given patients with CHD are generally older, it is possible that a subtle survival bias may still be influencing our findings, although all analyses were adjusted for age. However, based on simulation modeling, sample size, and projected single nucleotide polymorphism effect size, we and others have previously estimated that selection biases are only minimal—operating in this context and would be unlikely to account for our observed findings. Although our findings potentially argue against important selection biases in the analysis for the primary outcome, they are relatively insensitive assessments and may not fully elucidate such biases.

Possible biological explanations could also exist for our findings. Pathological studies indicate differences between chronic stable atherosclerotic plaques that cause ischemia through progressive vessel occlusion and vulnerable plaques with thin caps, prone to sudden plaque rupture, unheralded MI, and coronary deaths. In a seminal study dissecting the phenotype of CHD, a lack of effect for chromosome 9p21 and MI was noted, when both cases and controls had underlying atherosclerosis. Our group and others have in parallel shown that chromosome 9p21 robustly associates with atherosclerotic phenotypes, whereas functional studies have also implicated this region with molecular activity that drives atheroma. Furthermore, in this study, we show that the only outcome positively associated with chromosome 9p21 is incident revascularization, perhaps reflecting more severe atherosclerosis burden. Collectively, these data support the concept that chromosome 9p21 promotes progressive atheroma formation and does not confer risk via plaque rupture.

In this context, it is worth noting that chromosome 9p21 associates more robustly with CHD in case-control studies than in prospective cohort studies. The difference, as proposed by others, could hypothetically be accounted for by incidence-prevalence bias, with chromosome 9p21 carriers more likely to survive a CHD event and thus be over represented among CHD cases (the opposite to survival bias described above). This becomes more likely as stated above if chromosome 9p21 drives a more progressive and stable atheroma phenotype. If this holds true, then among survivors with established CHD, one might expect that chromosome 9p21 carriers could hold a small favorable advantage over those who experience CHD in its absence, due instead to other more dangerous or vulnerable characteristics, and despite undergoing more subsequent revascularization, these chromosome 9p21 carriers do not experience more dangerous or fatal events.

These findings have important implications. Clinically, they indicate that a degree of caution should be applied when considering or evaluating patients for chromosome 9p21 to predict disease progression or residual risk. They also highlight the need to appreciate important biases that may inflate or attenuate association findings in the setting of subsequent events for individuals with established disease. Mechanistically, these findings support existing and emerging efforts seeking to elucidate the mechanism of the most robust genetic discovery for CHD in recent decades.

There are important limitations to consider. First, among individuals in GENIUS with established CHD,
the timing of the first CHD event or age of onset was often unknown, so we could not account for this variable in our analyses. However, the lack of association in the acute coronary syndrome studies, which had documented timing of the first event, suggests this did not impact the findings. Second, we had limited information on whether subsequent revascularization events were late staged procedures, which would count as part of the index CHD event or unplanned and symptom driven and thereby a true subsequent event, which may have diluted the effect estimate. Third, although we did not observe a specific interaction for statin or aspirin use, we cannot rule out an effect of combined or additional medication usage attenuating the association signal, given the high prevalence of secondary prevention drug use in this setting compared with general population cohorts. Fourth, our analyses were restricted to participants of European descent as most of the included studies only recruited these individuals, and so we were markedly underpowered to explore associations in other ethnic groups. Unfortunately, this remains a wider problem of genetic research and global efforts are ongoing to address this imbalance. Finally, variability of follow-up duration across studies is an analytical challenge and could have impacted our findings, through misclassification. However, a sensitivity analysis stratifying on the follow-up duration of individual studies (<5 or ≥5 years) revealed minimal evidence (P=0.62) of heterogeneity in effect estimates (Figure V in the Data Supplement), suggesting that this is unlikely to have influenced our findings significantly as effect estimates were concordant across studies with different lengths of follow-up. Our major strengths, however, include the size of the study and the large number and types of subsequent events and an effort to examine for selection biases. We also sought to mitigate potential miscoding of the risk allele, given rs1333049 is a palindromic single nucleotide polymorphism, and also the risk allele C changes from being a minor allele in population cohorts to the major allele in CHD cohorts. Finally, this analysis benefited from the collective expertise and input of over 170 investigators and analysts, many of whom have previously reported on chromosome 9p21.

In conclusion, using the newly formed GENIUS-CHD consortium, we demonstrate that variation at chromosome 9p21 shows no clear association with risk of subsequent CHD events when all individuals have established CHD at baseline. This is in marked contrast to prior case-control studies examining odds of CHD presence compared with disease-free controls. We could not account for the attenuation of effect in terms of selection biases or subgroup effects. However, we did find a greater risk for incident revascularization in those with established CHD, and although residual bias may be at play, our findings collectively support the view that chromosome 9p21 promotes CHD through progressive stable atheroma rather than through development of an unstable phenotype.
Acknowledgments

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