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 analyzing 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 (R²>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...
| Alias        | Cohort                                                                 | Total N genotyped | Study Design | CHD Type | Male, % | Age, y, SD | BMI (SD) | Diabetes mellitus, % | Smoking, % | Systolic BP, SD | Total Cholesterol, SD | Statin use, % | Creatinine, SD | Prior Revasc, % | Prior MI, % | PubMED ID |
|--------------|------------------------------------------------------------------------|-------------------|--------------|----------|---------|------------|----------|---------------------|------------|-------------------|------------------------|---------------|---------------|------------------|-------------|-----------|
| 4C           | Clinical Cohorts in Coronary disease Collaboration (4C)                | 1538              | Cohort CAD   | CAD      | 62.1    | 62.2 (11.95) | 30.2 (5.67) | 23.4                | ...         | 133.9 (23.7)     | 4.69 (1.10)            | 26.4          | 99.3 (83.2)   | 22.6             | 15.5        | ...       |
| AGNES        | Arrhythmia Genetics in the Netherlands                                | 1316              | Cohort ACS   | ACS      | 79.3    | 57.7 (10.81) | 26.5 (3.87) | 7.6                 | 59.3       | 5.28 (1.04)      | ...                      | 9.8           | ...           | ...              | ...         | 20622880 |
| ANGES        | Angiography and Genes Study                                          | 588               | Cohort Mixed | Mixed    | 65.5    | 64.1 (9.55)  | 28.1 (4.36) | 30.8                | 14.7       | 4.84 (0.84)      | 69.4                    | 83.0 (32.0)   | 42.4          | 24.7             | ...         | 21640993 |
| ATV8         | Italian Atherosclerosis, Thrombosis and Vascular Biology Group       | 1465              | Cohort ACS   | ACS      | 90.4    | 40.0 (4.40)  | 26.8 (4.07) | 8.4                 | 78.7       | 132.3 (20.6)     | 5.76 (1.39)            | 56.2          | ...           | ...              | ...         | 21757122 |
| C AB Genomics | Coronary Artery Bypass Genomics                                      | 1542              | Cohort Mixed | Mixed    | 80.1    | 64.7 (10.08) | 29.7 (5.71) | 10.1                | 11.2       | 4.21 (0.95)      | 75.2                    | ...           | ...           | 42.8             | ...         | 25649697 |
| C DC S       | Coronary Disease Cohort Study                                        | 1800              | Cohort ACS   | ACS      | 71.5    | 67.5 (11.96) | 27.3 (4.66) | 15.4                | 5.8        | 129.2 (21.6)     | 5.00 (1.09)            | 46.5          | 100.5 (40.0)  | 26.9             | 30.3        | 20400779 |
| C OR OGENE   | Corogene Study                                                        | 1489              | Cohort ACS   | ACS      | 70.9    | 64.7 (11.87) | 27.6 (4.84) | 18.2                | 34.4       | 4.63 (0.99)      | 5.2                     | 84.0 (44.3)   | ...           | ...              | ...         | 21642350 |
| CT MM        | Circulating Cells                                                     | 605               | Cohort Mixed | Mixed    | 68.9    | 63.0 (9.83)  | 27.6 (4.45) | 20.7                | 20.7       | 135.4 (19.1)     | 4.43 (1.05)            | ...           | 86.4 (34.9)   | 30.1             | ...         | 23975238 |
| C URE        | Cure-Genetics Study                                                  | 4242              | RCT ACS      | ACS      | 59.3    | 64.7 (10.99) | 27.9 (4.44) | 19.9                | 22.6       | 135.7 (21.9)     | ...                     | 93.0 (33.9)   | 13.9          | 31.8             | ...         | 11102254 |
| EG C U T     | Estonian Biobank                                                      | 2408              | Cohort CAD   | CAD      | 51.0    | 67.1 (10.88) | 28.9 (5.16) | 18.7                | 19.2       | 135.6 (18.0)     | 5.64 (1.17)            | 27.3          | ...           | 15.7             | 36.0        | 24518929 |
| EM ORY       | Emory Cardiovascular Biobank                                           | 2411              | Cohort Mixed | Mixed    | 70.1    | 64.5 (11.06) | ...           | 30.7                | 9.8        | 4.49 (1.02)      | 76.0                    | 99.0 (45.1)   | 61.7          | 27.9             | ...         | 20729229 |
| E RICO       | Estrategia de Registro de Insuficiencia Coronariana                   | 438               | Cohort ACS   | ACS      | 55.5    | 63.8 (13.36) | 27.0 (5.06) | 39.1                | 31.0       | 99.2 (38.4)      | ...                     | ...           | 23.8          | ...              | 11.3        | 23644870 |
| FINCA VA S   | Finnish Cardiovascular Study                                         | 1671              | Cohort Mixed | Mixed    | 69.4    | 60.9 (11.03) | 27.8 (4.35) | 18.4                | 24.3       | 140.2 (22.1)     | 4.74 (0.90)            | 57.3          | 90.8 (66.8)   | 32.6             | 39.0        | 16515696 |
| FR ISC II    | FRISC II Study                                                        | 3106              | RCT ACS      | ACS      | 69.4    | 66.2 (9.80)  | 26.8 (3.87) | 12.7                | 27.1       | 143.3 (22.4)     | 5.80 (1.12)            | 12.3          | 90.6 (18.8)   | 12.1             | 27.2        | 10475181 |
| G END EM IP  | Genetic Determination of Myocardial Infarction in Prague              | 1267              | Cohort ACS   | ACS      | 75.8    | 56.4 (8.63)  | 28.6 (4.68) | 18.8                | 60.8       | 137.0 (20.8)     | 5.51 (1.17)            | 16.6          | ...           | 29.7             | 41.6        | 23249639 |
| G EN E Bank  | Cleveland Clinic Genebank Study                                      | 2345              | Cohort Mixed | Mixed    | 74.3    | 61.5 (11.06) | 29.4 (5.44) | 11.8                | 16.8       | 132.7 (21.1)     | 4.46 (0.93)            | 71.8          | ...           | 65.3             | 56.1        | 21475195 |
| GENESIS-PRAXY | Gender and Sex Determinants of Cardiovascular Disease: From Bench to Beyond-Premature Acute Coronary Syndrome | 784               | Cohort ACS   | ACS      | 69.2    | 48.3 (5.62)  | ...           | 13.8                | 44.2       | 139.5 (26.5)     | 4.85 (1.18)            | 93.1          | 75.9 (19.7)   | 11.3             | 11.4        | 22607849 |

(Continued)
| Alias          | Cohort | Study Type | N genotyped | PubMED ID |
|---------------|--------|------------|-------------|-----------|
| GENOCOR       | Cohort | Mixed      | 497         | 22773231  |
| GoDARTS       | Cohort | Mixed      | 1003        | 80299245  |
| GENOCOR       | Cohort | Mixed      | 2000        | 80299245  |
| GoDARTS       | Cohort | ACS        | 699         | 80299245  |
| GENOCOR       | Cohort | ACS        | 1086        | 80299245  |
| GoDARTS       | Cohort | ACS        | 6223        | 80299245  |
| GENOCOR       | Cohort | ACS        | 2145        | 80299245  |
| GENOCOR       | Cohort | Mixed      | 6763        | 80299245  |
| GoDARTS       | Cohort | RCT        | 704         | 80299245  |
| GENOCOR       | Cohort | Mixed      | 1147        | 80299245  |
| GoDARTS       | Cohort | RCT        | 4390        | 80299245  |
| JUMC          | Cohort | Mixed      | 704         | 80299245  |
| KAROLA         | Cohort | Mixed      | 1147        | 80299245  |
| LIFE-Heart     | Cohort | Mixed      | 2175        | 80299245  |
| INTERMOUNTAIN  | Cohort | Mixed      | 603         | 80299245  |
| NE_POLAND     | Cohort | Mixed      | 603         | 80299245  |
| NEAPOLIS      | Cohort | Mixed      | 393         | 80299245  |
| OHGS          | Cohort | Mixed      | 1390        | 80299245  |
| PMI           | Cohort | ACM        | 1390        | 80299245  |
| Alias | Cohort | Design | CHD Type | Total N genotyped | Age, y, SD BMI (SD) | Diabetes mellitus, % | Smoking, % | Systolic BP, SD | Total cholesterol, SD | Statin use, % | Creatinine, SD | Prior MI, % | Prior Revasc, % |
|-------|--------|--------|----------|------------------|--------------------|---------------------|-------------|----------------|-------------------|---------------|---------------|------------|--------------|
| POPULAR | The Popular Study | RCT | ACS | 997 | 74.3 (10.00) | 18.9 | 31.1 | 43.7 | 8.25 (0.64) | 80.7 | 26.5 (4.86) | 80.7 | 26.5 (4.86) |
| PROSPER | Prospor Study | RCT | CAD | 439 | 69.9 (10.31) | 10.3 | 16.2 | 34.7 | 10.40 (0.64) | 26.0 | 85.9 | 10.94 (0.62) | 85.9 | 26.0 |
| SHEEP | Sheep Study | RCT | CAD | 1052 | 75.9 (10.10) | 19.8 | 30.4 | 46.6 | 100.6 (28.6) | 28.2 | 27.9 | 185.49 (20.2) | 27.9 | 185.49 (20.2) |
| SMART | Smaert Study | RCT | CAD | 2485 | 82.2 (10.00) | 16.6 | 24.4 | 137.4 (19.8) | 4.7 (0.96) | 75.7 | 29.3 | 22.7 | 43.6 | 104.68 (21.6) |
| STABILITY | Stabilite Study | RCT | CAD | 9287 | 82.0 (10.10) | 18.2 | 50.0 | 131.8 (20.6) | 4.7 (0.96) | 74.6 | 21.5 | 16.7 | 51.5 | 24.4 (4.86) |
| THI | Thi Study | RCT | CAD | 77.3 | 63.6 (10.00) | 30.5 | 21.3 | 113.0 (19.8) | 4.7 (0.96) | 74.6 | 21.5 | 16.7 | 51.5 | 24.4 (4.86) |
| TNT | Tin Study | RCT | CAD | 71.3 | 63.6 (10.00) | 30.5 | 21.3 | 113.0 (19.8) | 4.7 (0.96) | 74.6 | 21.5 | 16.7 | 51.5 | 24.4 (4.86) |
| TRIUMPH | Triumph Study | RCT | CAD | 77.3 | 63.6 (10.00) | 30.5 | 21.3 | 113.0 (19.8) | 4.7 (0.96) | 74.6 | 21.5 | 16.7 | 51.5 | 24.4 (4.86) |
| THI | Thi Study | Mixed | ACS | 71.3 | 63.6 (10.00) | 30.5 | 21.3 | 113.0 (19.8) | 4.7 (0.96) | 74.6 | 21.5 | 16.7 | 51.5 | 24.4 (4.86) |
| TNT | Tin Study | Mixed | ACS | 71.3 | 63.6 (10.00) | 30.5 | 21.3 | 113.0 (19.8) | 4.7 (0.96) | 74.6 | 21.5 | 16.7 | 51.5 | 24.4 (4.86) |
| TRIUMPH | Triumph Study | Mixed | ACS | 71.3 | 63.6 (10.00) | 30.5 | 21.3 | 113.0 (19.8) | 4.7 (0.96) | 74.6 | 21.5 | 16.7 | 51.5 | 24.4 (4.86) |
| THI | Thi Study | Cohort | ACS | 71.3 | 63.6 (10.00) | 30.5 | 21.3 | 113.0 (19.8) | 4.7 (0.96) | 74.6 | 21.5 | 16.7 | 51.5 | 24.4 (4.86) |
| TNT | Tin Study | Cohort | ACS | 71.3 | 63.6 (10.00) | 30.5 | 21.3 | 113.0 (19.8) | 4.7 (0.96) | 74.6 | 21.5 | 16.7 | 51.5 | 24.4 (4.86) |
| TRIUMPH | Triumph Study | Cohort | ACS | 71.3 | 63.6 (10.00) | 30.5 | 21.3 | 113.0 (19.8) | 4.7 (0.96) | 74.6 | 21.5 | 16.7 | 51.5 | 24.4 (4.86) |

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; RCT, randomized controlled trial; and WTCCC, Welcome 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).

**Table 1.** Association between chromosome 9p21 and secondary outcomes in participants with baseline CHD, within GENIUS-CHD (Genetics of Subsequent Coronary Heart Disease).

All meta-analysis estimates were adjusted for age and sex. CHD indicates coronary heart disease; CVD, cardiovascular disease; MI, myocardial infarction; and OR, odds ratio.
Secondary Outcomes

We additionally examined the association between chromosome 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 revascularization during follow-up was 1.07 (95% CI, 1.04–1.09). The effect on the composite outcome of any cardiovascular 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 protection 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 chromosome 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 risk allele frequencies with advancing age, relative to younger carriers (Figure VI in the Data Supplement).

DISCUSSION

In this study, we examined the effect of genetic variation at the chromosome 9p21 locus on risk of subsequent events in 103,357 individuals with established CHD using the newly formed GENIUS-CHD consortium.8 We found that (1) in contrast to the known strong association with CHD observed in CARDIoGRAMPlusC4D, 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 evidence 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 replicated 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.6 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 established CHD, and reported no clear evidence of an effect of variants at chromosome 9p21 on the risk of subsequent 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 chromosome 9p21 in subsequent CHD event risk, revealing a clear lack of association with a common composite coronary end point. This is in marked contrast to findings from studies comparing cases to CHD-free controls, as confirmed through meta-analysis of CARDIoGRAMPlusC4D data. Furthermore, we were able to...
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 (i.e., 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 findings in the setting of subsequent events for individuals with established disease. Mechanistically, 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 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 benefitted 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 effects 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.
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Patel et al; Chromosome 9p21 and Subsequent CHD Events

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