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Clinical Conditions and Their Impact on Utility of Genetic Scores for Prediction of Acute Coronary Syndrome

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BACKGROUND: Acute coronary syndrome (ACS) is a clinically significant presentation of coronary heart disease. Genetic information has been proposed to improve prediction beyond well-established clinical risk factors. While polygenic scores (PS) can capture an individual’s genetic risk for ACS, its prediction performance may vary in the context of diverse correlated clinical conditions. Here, we aimed to test whether clinical conditions impact the association between PS and ACS.

METHODS: We explored the association between 405 clinical conditions diagnosed before baseline and 9080 incident cases of ACS in 387,832 individuals from the UK Biobank. Results were replicated in 6430 incident cases of ACS in 177,876 individuals from FinnGen.

RESULTS: We identified 80 conventional (e.g., stable angina pectoris and type 2 diabetes) and unconventional (e.g., diaphragmatic hernia and inguinal hernia) associations with ACS. The association between PS and ACS was consistent in individuals with and without most clinical conditions. However, a diagnosis of stable angina pectoris yielded a differential association between PS and ACS. PS was associated with a significantly reduced (interaction \(P = 2.87 \times 10^{-8}\)) risk for ACS in individuals with stable angina pectoris (hazard ratio, 1.163 [95% CI, 1.082–1.251]) compared with individuals without stable angina pectoris (hazard ratio, 1.531 [95% CI, 1.497–1.565]). These findings were replicated in FinnGen (interaction \(P = 1.38 \times 10^{-6}\)).

CONCLUSIONS: In summary, while most clinical conditions did not impact utility of PS for prediction of ACS, we found that PS was substantially less predictive of ACS in individuals with prevalent stable coronary heart disease. PS may be more appropriate for prediction of ACS in asymptomatic individuals than symptomatic individuals with clinical suspicion for coronary heart disease.

Key Words: acute coronary syndrome • diagnosis • genetics • heart diseases

Acute coronary syndrome (ACS), including myocardial infarction, is an unstable consequence of coronary heart disease (CHD), the leading cause of death worldwide. In Europe, CHD accounts for 1.8 million deaths per year, making up almost 20% of all cardiovascular disease-related deaths. Thus, prediction of ACS and prevention of CHD remain major public health issues.

Well-established clinical risk factors, such as type 2 diabetes and hypercholesterolemia, are highly predictive of future health outcomes, including ACS. Individuals with an accumulation of such risk factors are candidates for preventative statin interventions per American and European guidelines. Recently, other risk-enhancing factors independently associated with...
ACS have been proposed to improve prediction of ACS and inform statin intervention decisions.\(^5\text{-}^8\) Several studies have effectively used machine learning approaches to leverage electronic health records for prediction of cardiovascular diseases,\(^6\text{-}^9\text{-}^{15}\) and unbiased, comprehensive analyses of diverse correlated clinical conditions in large-scale biobanks may continue to better inform prediction of ACS.

Furthermore, genetic information may inform prediction of ACS beyond well-established clinical risk factors.\(^20\text{-}^25\) Currently, guidelines on evaluating risk for ACS and initiating statin interventions rely on several well-established clinical risk factors but do not support the use of genetic information. However, genetic information has the advantage of remaining stable throughout life and, therefore, could be used to improve earlier prediction of ACS.\(^21\text{-}^23\) Results from large genome-wide association studies can be used to derive polygenic scores (PS) based on millions of single nucleotide polymorphisms that are robustly associated with CHD.\(^24\) Several studies have investigated the use of PS for prediction of ACS in addition to well-established clinical risk factors.\(^20,25\text{-}^27\) However, there are no studies to date that examine the association between PS and ACS in the context of diverse correlated clinical conditions.

In this study, we have 2 main goals that we assessed in 2 large-scale biobanks. First, we aimed to comprehensively explore the association of clinical conditions with ACS. Second, we aimed to assess whether clinical conditions associated with ACS impact the association between PS and ACS to provide context for the use of PS for prediction of ACS.

### METHODS

Full methods are available in the Data Supplement. Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to the UK Biobank or FinnGen at access@ukbiobank.ac.uk or finngen-info@helsinki.fi, respectively. This study was approved by an institutional review committee, and subjects gave informed consent.

### RESULTS

#### Several Clinical Conditions Are Associated With ACS

In the UK Biobank, we explored the association between 405 clinical conditions diagnosed before baseline and 9080 cases of ACS out of 387832 individuals (Table; exclusion criteria in Table I in the Data Supplement) and identified 80 clinical conditions that were significantly (\(P<1.23\times10^{-4}\)) associated with ACS after multiple testing correction (Figure 1). The 80 associated clinical conditions had an average hazard ratio of 2.4 for ACS. Some of these associations were conventional (eg, stable angina pectoris [SAP] and type 2 diabetes), and others were unconventional (eg, diaphragmatic hernia and inguinal hernia). Adjustment for measured risk factors modestly reduced the association, but statistical significance was retained for all 80 clinical conditions. Table II in the Data Supplement includes all 80 clinical conditions that were associated with ACS before and after adjustment for measured risk factors. This analysis was replicated in FinnGen, in which we explored the association between 645 clinical conditions and 6430 cases of ACS out of 177876 individuals (Table; exclusion criteria in Table I in the Data Supplement) and identified 71 clinical conditions that were significantly (\(P<7.75\times10^{-5}\)) associated with ACS after multiple testing correction (Figure 1 in the Data Supplement). The 71 associated clinical conditions had an average hazard ratio of 2.1 for ACS. Table III in the Data Supplement includes all 71 clinical conditions that were associated with ACS. Thirty-three clinical conditions were associated with ACS in both the UK Biobank and FinnGen. For these clinical conditions, we observed good consistency (\(R^2=0.65\)) between the association observed in the UK Biobank and FinnGen, suggesting the generalizability of these associations across 2 large-scale biobanks (Figure II in the Data Supplement).

#### Most Clinical Conditions Do Not Impact Association Between PS and ACS Except for SAP

First, we confirmed that PS was associated with ACS in the UK Biobank (HR for 1 SD increase in PS=1.49 [95% CI, 1.46\text{-}1.53], \(P=1.36\times10^{-294}\)) and FinnGen (HR for 1 SD increase in PS=1.44 [95% CI, 1.40\text{-}1.47], \(P=1.71\times10^{-146}\)). Next, we aimed to understand the value of measuring PS in individuals without ACS at baseline and whether the association between PS and ACS changed given the diagnosis of certain clinical conditions. We tested for the interaction between PS and 80 clinical conditions that were associated with ACS in the UK Biobank and identified a significant interaction (\(P=2.87\times10^{-4}\)) between SAP and PS (Figure 2). Here,
SAP was defined as angina pectoris with documented spasm, other forms of angina pectoris, and unspecified angina pectoris (International Classification of Disease, Tenth Revision codes I20.1, I20.8, and I20.9). This was the only interaction ($P=1.38 \times 10^{-6}$) that was replicated in FinnGen (Figure III in the Data Supplement). In the UK Biobank, there were 5477 cases of SAP (prevalence=1.41%), and in FinnGen, there were 8326 cases of SAP (prevalence=4.68%). There was also a significant interaction between PS and type 2 diabetes ($P=6.01 \times 10^{-19}$) in the UK Biobank, but this interaction was not significant after multiple testing correction in FinnGen ($P=5.00 \times 10^{-12}$).

In the UK Biobank, individuals with SAP had a significantly reduced risk for ACS (HR for 1 SD=1.163 [95% CI, 1.082–1.251]) compared with individuals without SAP (HR for 1 SD=1.531 [95% CI, 1.497–1.565]; Figure 3). All individuals, with or without SAP, did not have ACS at baseline, as individuals with ACS at baseline were excluded from the analysis. In a model including measured risk factors in the UK Biobank, results remained consistent (SAP HR=1.159 [95% CI, 1.078–1.246] and no SAP HR=1.488 [95% CI, 1.455–1.522], interaction $P=2.05 \times 10^{-7}$). This observation was replicated in FinnGen, and individuals with SAP had a significantly reduced risk for ACS (HR for 1 SD=1.448 [95% CI, 1.407–1.490]). PS was also strongly associated with SAP in the UK Biobank (HR, 1.44 [95% CI, 1.40–1.48], $P=3.66 \times 10^{-148}$) and FinnGen (HR, 1.47 [95% CI, 1.42–1.49], $P=3.12 \times 10^{-228}$). Importantly, PS was also strongly associated with SAP in individuals who did not develop ACS in the UK Biobank (HR, 1.45 [95% CI, 1.41–1.48], $P=4.45 \times 10^{-122}$) and FinnGen (HR, 1.44 [95% CI, 1.40–1.48], $P=6.05 \times 10^{-199}$), suggesting that there is a large overlap in the genetic basis of SAP and ACS.

We also noticed that the association between measured risk factors and ACS was generally weaker among individuals with SAP than individuals without SAP (Table IV in the Data Supplement). For example, there was no association between total cholesterol and ACS in individuals with SAP (HR, 0.96 [95% CI, 0.89–1.03], $P=0.247$), but there was an association in individuals without SAP (HR, 1.11 [95% CI, 1.09–1.13], $P=6.43 \times 10^{-28}$).

### Sensitivity Analyses

We performed several sensitivity analyses. First, because PS has been shown to have age-dependent effects and individuals with SAP tended to be older and include more males than individuals without SAP, we performed an age- and sex-matched analysis to test whether differences in age or sex explained the differential association of PS and ACS. After matching age and sex distributions in individuals with and without SAP, the interaction between SAP and PS remained significant in both the UK Biobank (interaction $P=1.51 \times 10^{-3}$) and FinnGen (interaction $P=1.16 \times 10^{-2}$). We also adjusted our analysis for diabetes, and the interaction between SAP and PS remained significant in both the UK Biobank (interaction $P=1.07 \times 10^{-10}$) and FinnGen (interaction $P=3.77 \times 10^{-4}$).

Second, because many well-established guidelines suggest statin interventions for individuals with SAP, we adjusted our analysis for statin use to explore whether statin use in individuals with SAP lowered the association with ACS. Statin use in the UK Biobank was self-reported, and statin use in FinnGen was defined using high-quality prescription registries. In the UK Biobank, 82.1% of individuals with SAP used statins and 15.9% of individuals without SAP used statins. In FinnGen, 81.7% of individuals with SAP used statins and 27.8% of individuals without SAP used statins. The interaction between SAP and PS remained significant after adjusting for statin use in both the UK Biobank (interaction $P=1.20 \times 10^{-10}$) and FinnGen (interaction $P=3.77 \times 10^{-4}$). In the UK Biobank, the interaction between SAP and PS remained significant ($P=7.39 \times 10^{-4}$) after removing statin users. In FinnGen, the interaction between SAP and PS remained significant ($P=3.85 \times 10^{-4}$) after adjusting for additional prescriptions, including statins, aspirins (ATC code B01AC06), all β-blockers (ATC code C07AB), and all angiotensin-converting enzyme inhibitors (ATC code C09AA). However, given the high prevalence of prescription usage in this patient population compared to the general population, we cannot eliminate the possibility of an additive effect from additional prescriptions that were not considered in this analysis.

Third, we increased the time window between a diagnosis of SAP and an ACS event to reduce the chances...
of capturing the same underlying cardiovascular event. Increasing the time window from 30 days to 300 and 500 days only modestly reduced the interaction between SAP and PS in the UK Biobank (300 days $P=5.14\times10^{-11}$ and 500 days $P=3.76\times10^{-11}$) and FinnGen (300 days $P=5.83\times10^{-4}$ and 500 days $P=1.86\times10^{-3}$). Average and median time between an SAP diagnosis and an ACS event was 9.1 and 8.9 years, respectively, in the UK Biobank. Similarly, average and median time was 6.7 and 5.7 years, respectively, in FinnGen. This suggested that the cases of SAP captured in our study were diagnosed earlier and independent of the events of ACS.

Fourth, we examined the interaction between SAP and ACS in different ancestry groups. Our cohort from the UK Biobank included individuals of African ($n=5543$), Ad Mixed American ($n=820$), Central and South Asian ($n=6976$), East Asian ($n=2196$), European ($n=339771$), and Middle Eastern ($n=1258$) ancestry. In Central and South Asian (ACS cases=306, SAP diagnoses=194, $P=1.14\times10^{-2}$) and European (ACS cases=7969, SAP diagnoses=4810, $P=2.36\times10^{-11}$), the interaction between SAP and PS remained significant. Other ancestry groups, which included <100 diagnoses of SAP and 100 cases of ACS, were not analyzed due to the lack of statistical power.

Figure 1. Association between 405 clinical conditions and 9080 cases of acute coronary syndrome unadjusted and adjusted for measured risk factors from the UK Biobank. We used time-varying covariate Cox survival models (A), and adjusted for age, sex, and principal components (B). Measured risk factors included body mass index, systolic blood pressure, smoking status, high-density lipoprotein cholesterol, and total cholesterol. Red dotted line is the significance threshold after multiple testing correction ($P<1.23\times10^{-4}$). Top 10 clinical conditions are labeled.
Fifth, we considered the possibility that the significant interaction between SAP and PS was simply capturing underlying differences in risk factor distribution between individuals with and without SAP. If this was the case, we would observe significant interactions between PS and cardiovascular risk factors. We tested for the interaction between PS and body mass index (BMI), systolic blood pressure, smoking status, HDL (high-density lipoprotein) cholesterol, and total cholesterol. There were no significant interactions between PS and measured risk factors, except for BMI (interaction \( P = 8.30 \times 10^{-3} \)). However, the effect size change was minimal for the interaction between BMI and PS (SAP HR=1.031 [95% CI, 1.017–1.045]; no SAP HR=1.047 [95% CI, 0.9979–1.008]).

Figure 2. Interaction between polygenic score (PS) and 80 clinical conditions significantly \( (P < 1.23 \times 10^{-4}) \) associated with acute coronary syndrome (ACS) after multiple testing correction from the UK Biobank. Red dotted line is the significance threshold \( (P < 1.23 \times 10^{-4}) \). Top 10 clinical conditions are labeled. There was a significant interaction between stable angina pectoris (SAP) and PS in association with ACS \( (P = 2.87 \times 10^{-8}) \) that was replicated in FinnGen \( (P = 1.38 \times 10^{-6}) \). There was also a significant interaction between SAP and type 2 diabetes \( (P = 6.01 \times 10^{-4}) \) in the UK Biobank, but this interaction was not significant after multiple testing correction in FinnGen \( (P = 5.00 \times 10^{-2}) \).

Prediction Performance of PS Differs Between Individuals With and Without SAP

We examined the Harrell C index to evaluate the prediction performance of PS (Figure 4). In the UK Biobank, individuals with SAP had a C index for PS of 0.606 (95% CI, 0.595–0.616) and individuals without SAP had a C index for PS of 0.747 (95% CI, 0.743–0.750) in models adjusted for age, sex, principal components, BMI, systolic blood pressure, smoking status, HDL cholesterol, and total cholesterol. These findings were replicated in FinnGen, and individuals with SAP had a C index of 0.665 (95% CI, 0.655–0.674) and individuals without SAP had a C index of 0.825 (95% CI, 0.821–0.830). The lower C index in individuals with SAP was explained by the lower association between established cardiovascular risk factors, including age, and ACS in these individuals.

Because it is easier to obtain a higher improvement in predictive performance (ΔAC index) when the baseline model has a lower prediction performance,28,29 we expected the improvement in C index due to PS to be higher in individuals with SAP. Nevertheless, the addition of PS to measured risk factors increased the C index more in individuals without SAP (AC index=0.021) than...
in individuals with SAP ($\Delta C$ index=0.010). In FinnGen, PS increased the C index by 0.012 in individuals without SAP and by 0.013 in individuals with SAP. Last, we calculated the net reclassification index (NRI) to evaluate the improvement in reclassification when adding PS to the baseline prediction performance of measured risk factors (Table V in the Data Supplement). Addition of PS significantly improved the prediction performance in individuals without SAP (categorical NRI=0.116, $P <1.00 \times 10^{-3}$; continuous NRI=0.315, $P <1.00 \times 10^{-3}$) but not in individuals with SAP (NRI=0.038, $P =0.187$; continuous NRI=0.113, $P =3.41 \times 10^{-3}$). Overall, the NRI was higher among individuals without SAP compared with individuals with SAP.

DISCUSSION

In this study, we performed an unbiased, comprehensive evaluation of the association between diverse correlated clinical conditions and ACS across 2 large-scale biobanks. Moreover, by exploring the impact of clinical conditions on the association between PS and ACS, we provided context for the use of PS for prediction of ACS.

First, we found that a large number of clinical conditions were associated with ACS, independent of measured risk factors. Using clinical conditions to predict risk for ACS may be more convenient than using measured risk factors because this information is easily accessed and obtained from electronic health records and does not require in-person visits. In addition to well-established clinical risk factors, such as type 2 diabetes, that are routinely considered, additional clinical conditions that are associated with ACS may be taken into consideration when evaluating risk for ACS. Identification of such clinical conditions is critical to provide a comprehensive, well-informed assessment of risk for ACS.

Second, by using a hypothesis-free approach across 80 clinical conditions associated with ACS, we found that the association between PS and ACS was consistent across individuals with or without most of these clinical conditions. Diagnosis of a clinical condition did not change the association between PS and ACS, suggesting that clinical conditions do not impact the utility of PS. Previous work has shown that different groups of individuals may benefit more from measuring PS than other groups. For example, previous work has shown that PS was more predictive of ACS among nonsmokers. However, in our study, we generally found that the diagnosis of a clinical condition did not affect the association between PS and ACS. The only differential association that was found in both the UK Biobank and FinnGen was a diagnosis of SAP, in which SAP was significantly more associated with ACS in individuals without a previous diagnosis of SAP than in individuals with a previous diagnosis of SAP.

There are at least 2 possible explanations for this phenomenon. First, progression of ACS may occur with or without the presentation of SAP. It is possible that individuals who develop ACS with or without prior SAP are clinically and genetically distinct. It is widely accepted that ACS varies in clinical presentation, and other studies have explored the significance of a diagnosis of SAP before ACS. For example, other studies have found that individuals with prior SAP had more extensive atherosclerosis and a greater prevalence of clinical risk factors, such as hypertension, than individuals without prior SAP who developed ACS. In another study, myocardial infarction was the most common first clinical presentation in individuals without prior SAP who developed ACS. Other studies have also found that individuals with prior SAP had a more favorable prognosis compared with individuals without prior SAP who developed ACS. In our study, we found a differential association between PS and ACS in individuals with and without SAP, further suggesting that these individuals may be clinically and genetically distinct. Taken together, there may be different pathways of progression of ACS that may warrant different assessments and interventions.

Second, a diagnosis of SAP may be synonymous to a diagnosis of CHD. In a clinical setting, individuals with SAP often have already started developing CHD. Subsequently, individuals with SAP may already have a higher risk for ACS, and PS may not be as informative. As a result, PS may lose its prediction performance in individuals who have already been diagnosed with SAP. This observation is supported by other studies that have shown that prediction of secondary CHD events by PS is...
attenuated compared with that of primary CHD events.\textsuperscript{38} Indeed, we found that PS was strongly associated with SAP, suggesting that there is a large overlap in the genetic basis of SAP and ACS.

An open matter that may explain this phenomenon is index event bias. Index event bias may occur in studies that select patients based on the occurrence of an index event, and as a result, measured risk factors may have less of an effect on recurrent events.\textsuperscript{39–41} In our study, SAP may be an index event that decreased the prediction performance of PS in individuals with SAP compared with individuals without SAP. In other words, because ACS is dependent on multiple factors, such as underlying chronic conditions and measured risk factors, conditioning on a diagnosis of SAP creates a dependence between such factors. As a result, individuals with SAP do not require the same burden of increased measured risk factors and increased PS to develop ACS. As mentioned previously, individuals with SAP are more likely to have underlying chronic conditions, such as extensive atherosclerosis. This may entailing measured risk factors and PS do not need to have a large association with ACS to confer the same risk, due to the presence of such underlying chronic conditions. Indeed, our study showed that measured risk factors and PS were less associated with ACS in individuals with SAP, reflecting other studies that have also shown that individuals with SAP often have less associated measured risk factors.\textsuperscript{21} Additionally, we found that BMI was the only measured risk factor that had a significant, but modest, interaction with PS. Previous work has similarly examined whether index event bias affected the attenuated association of the chromosome 9p21 locus and subsequent CHD and found that BMI indeed modestly affected this association.\textsuperscript{42} While we excluded individuals with known ACS, our sensitivity analyses indicated that index event bias does not solely explain the effect size differences for SAP.\textsuperscript{39,43}

A few limitations of this study must be considered. First, the definition of ACS and clinical conditions were based on diagnostic codes derived from national health registries. Underreporting and incorrect use of diagnostic codes in a clinical setting are inherent to this type of data. Nevertheless, we obtained similar results in 2 large-scale biobanks from the United Kingdom and Finland. Additional evidence from other studies also supports the quality of this type of data.\textsuperscript{44–46} Future studies are needed to fully assess the validity of using registry-based clinical conditions across large-scale biobanks from different countries, but our study supports the feasibility of cross-nation registry-based analyses. Second, our PS represents a snapshot of current research in genetic scores. PS is inherently tied to the study used to construct the genetic scores, and as larger genome-wide association studies are conducted, genetic scores will necessarily improve and become more predictive. Therefore, our results represent a lower bound of prediction performance of PS, and it is likely that additional studies that improve genetic scores will improve the prediction performance of PS. Third, while our study included individuals from different ancestry groups, individuals from European ancestry comprised the majority of our cohort. Whether our findings generalize to non-European ancestry groups requires further study. This reflects a larger problem of the lack of diversity in genetic research and global efforts continue to address this problem.\textsuperscript{57}

CONCLUSIONS

Using an unbiased, comprehensive approach, we identified clinical conditions that were associated with ACS, independent of measured risk factors. Overall, we found that the association between PS and ACS remained consistent across many clinical conditions, suggesting that the utility of PS for prediction of ACS is largely independent of previous clinical conditions experienced by the patient. Nevertheless, we found one exception: individuals without SAP had a greater association between PS and ACS than individuals with SAP. In conclusion, we demonstrated that PS may be more appropriate for prediction of ACS among asymptomatic individuals than symptomatic individuals with clinical suspicion for CHD.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Materials

Supplemental Methods
Supplemental Tables I–V
Supplemental Figures I–III

References 48–56

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