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Polygenetic risk for coronary artery disease increases hospitalization burden and mortality

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ABSTRACT

Background: Coronary artery disease (CAD) is a leading cause of death worldwide and increasing cost for society. Genome wide association studies (GWAS) have identified common variants associated with CAD. Combining single nucleotide polymorphisms (SNPs) into a genetic risk score (GRS) can estimate an individual's genetic burden.
Objectives: To investigate whether GRS for CAD can predict hospitalization and mortality.
Methods: 23,594 individuals without CAD at baseline and with full data for all covariates from the population based prospective study Malmö diet and cancer study were investigated. The association between hospitalizations was calculated by negative binomial regression and risk of mortality was calculated by Cox proportional hazards regression. The GRS was constructed from 50 SNPs.
Results: The study population was divided into quintiles according to the value of GRS. During the mean follow-up time of 17.8 years, 17,254 individuals were hospitalized at least once. Individuals in the highest quintile of GRS were hospitalized 10% more often than individuals in the lowest quintile (IRR: 1.10 [95% CI 1.04–1.16], $p = 0.001$), mainly for cardiovascular reasons (IRR: 1.31 [95% CI 1.20–1.43], $p = 5.17 \times 10^{-10}$). These individuals had highly increased risk of CVD mortality (HR: 1.44 [1.25–1.66], $p = 6.56 \times 10^{-7}$) but not the risk of mortality due to other causes.
Conclusion: Our results suggest that genetic predisposition for CAD can predict hospitalization burden and mortality, especially due to cardiovascular causes, independently of traditional risk factors. As the risk conferred by the GRS is partially modifiable, our results may help to reduce societal costs, individual suffering and prolong life.

1. Introduction

The progress in Genome Wide Association Studies (GWAS) in recent years has led to discovery of many new polymorphisms associated with complex diseases, including coronary artery disease (CAD) [1–4]. The associated single nucleotide polymorphisms (SNPs) have each a relatively small individual effect size. However, we found that an aggregate of the 50 variants as a genetic risk score (CAD_GRS_50) has a substantial effect size when estimating the CAD genetic burden of an individual. After full adjustment for traditional risk factors, we found that individuals with high genetic risk (top quintile of the CAD_GRS_50) had a near doubling of the risk of CAD, compared to individuals with low genetic risk (bottom quintile of the GRS), resulting in a Net Reclassification Improvement of 17% [5].

Still, the clinical value of adding the CAD_GRS_50 to the traditional risk factors to better predict CAD has been debated as the genes per se cannot be changed with other than gene therapy, which given the polygenic nature of CAD is unlikely to ever be possible. Interestingly, however, even though only a few of the genes included in the CAD_GRS_50 act through elevating LDL-cholesterol, individuals with high genetic risk benefit the most from primary preventive therapy by statins and decrease both their absolute and relative risk to develop CAD [6]. The fact that the absolute risk reduction was greater among individuals with high genetic risk could be expected as the number of events prevented by statin therapy increases with cardiovascular risk in the population treated. However, the greater relative risk reduction in individuals with high genetic risk does in fact suggest that part of the genetic risk of CAD can be overcome by statin treatment. Thus, subjects with high genetic risk seem to respond better to statin therapy, and high genetic risk can be modified without changing the genes involved. In addition, subjects with high genetic risk were shown to have a markedly reduced risk of CAD if adherent to a healthy life style, as compared to an unhealthy life style, suggesting that also simple life style changes can overcome the genetic risk conferred by the CAD_GRS_50 [7]. Thus, surprisingly, the polygenetic risk of CAD seems to be modifiable to a large extent.

CVD is a leading cause of death, with 32% of all deaths worldwide and in Europe ≫4,000,000 people die due to cardiovascular causes

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[8–10]. Apart from individual suffering, CAD and its sequel are among the most common reasons for hospitalization and as such an enormous burden on health care system. In Sweden alone the cost of hospitalizations due to CVD causes is estimated to 13 billion Swedish crowns, but the total cost for CAD is estimated to 65 billion [11].

Here we set out to test the impact of the CAD_GRS_50 on prospective risk of hospitalizations. As we previously showed that the genetic risk of future CAD can be reduced by life style and statin therapy, we focused on the primary preventive setting, i.e. on individuals without CAD at baseline. Furthermore, as factors increasing the risk of premature death will reduce the risk of being hospitalized, we also investigated the CAD_GRS_50 in relation to mortality and made sensitivity analyses of the impact of CAD_GRS_50 on hospitalizations in survivors only.

2. Materials and methods

2.1. Study population

The Malmö Diet and Cancer study (MDC) is a large population based prospective study which had 30,447 participants drawn from 230,000 inhabitants from Malmö, Sweden. Individuals aged 45–73 years were recruited and underwent a baseline exam between 1991 and 1996. Details of this study have been described elsewhere [12,13]. We excluded subjects with CAD prior to the baseline exam ($n = 774$) and subjects with missing DNA or data on any of the covariates used in the fully adjusted models ($n = 6853$) which left us with a study population of 23,594 subjects. Clinical characteristics of study participants are shown in Table 1. We retrieved data on hospitalizations and mortality from Swedish National Inpatient registry and Swedish National Cause of Death Registry which covers 100% of the population. The data were available until December 31 2013. The causes of hospitalizations were classified according to ICD codes as the main diagnosis at discharge. The most common causes of CVD hospitalizations were ischeamic heart disease (33%), stroke (23%), arterial fibrillation (15%) and congestive heart failure (3%) as estimated from the causes of the first hospitalization event.

Data on the duration of each hospitalization was known for the 20 first hospitalizations of each individual. The total number of hospitalization days was calculated as a sum of all days in hospital for the first 20 stays. If there were ≫20 hospitalizations, we added the average number of hospitalization days derived from the first 20 for each additional hospitalization starting from the 21st.

2.2. Genotyping and GRS modelling

Genotypes of the MDC participants were determined using a multiplex method that combines polymerase chain reaction (PCR), allele-specific oligonucleotide ligation assays, and hybridization to oligonucleotides coupled to Luminex® 100TM xMAPTM microspheres (Luminex, Austin, TX) [14].

The weighted genetic risk score for CAD (CAD_GRS_50), consisting of 50 SNPs previously associated with CAD, for each individual was constructed by naturally log transforming the previously reported risk estimate for the modelled allele and multiplied by one for heterozygotes or two for homozygotes and summed [5]. Individuals were then divided according to their GRS into quintiles and analyzed as low genetic risk (Q 1, range 2.2–3.5), intermediate risk (Q2–4, range 3.6–3.9) and high genetic risk (Q5, range 4.0–5.7) in accordance with previous studies [5,6].

Table 1
Clinical characteristics of participants in MDC at baseline.

	Baseline characteristics
Number of individuals (males/females)	23,594 (8973/14621)
Age (years ± SD)	58 ± 7.7
Follow-up time (years ± SD)	17.8 ± 4.4
Smokers (%)	28.1
Diabetes (%)	4.0
Hypertension (%)	60.9
BMI (kg/m^2)	25.7 ± 4.0

2.3. Statistical analysis

All statistical analyses were performed in IBM SPSS Statistics 23 (IBM Corporation, Armonk, NY, USA).

Negative binomial regression has been used to relate the CAD_GRS_50 to all count variables (number of hospitalizations and number of hospitalization days). Two different models were used for analysis; model 1 was adjusted for age, sex and follow-up time while model 2 was adjusted for age, sex, follow-up time, hypertension, diabetes, smoking, ApoA1 and ApoB. Results are reported as incidence rate ratio (IRR) and 95% confidence interval. CAD_GRS_50 was related to mortality using Cox Proportional Hazards Model and to odds of ever being hospitalized using logistic regression, both with model 1 and model 2 adjustments as described above.

3. Results

3.1. Genetic CAD risk and number of hospitalizations during follow-up

The study population ($n = 23,594$) was divided according to their value of the genetic risk score (CAD_GRS_50) into quintiles and three groups were compared, individuals with low genetic risk (CAD_GRS_50 quintile 1, reference group), intermediate risk (CAD_GRS_50 quintiles 2–4) and high risk (CAD_GRS_50 quintile 5), in accordance with previous publications [5,6]. During the mean follow-up time of 17.8 years, 17,254 (73%) individuals were hospitalized at least once. The range of number of hospitalizations among subjects with at least one hospitalization was 1–110. In multivariate adjusted analyses (model 2) in the entire population, individuals with high genetic risk were hospitalized 10% more often and those with intermediate risk 7% more often compared to individuals with low genetic risk (Table 2). When comparing the effect sizes in the multivariate analysis (model 2), high genetic risk confers the same risk as approximately 2.5 years of age regarding number of hospitalizations (age per year: IRR 1.038 [1.036–1.041])]) and it conferred about half of the risk on number of hospitalizations as hypertension did (presence versus absence of hypertension; IRR 1.20 [1.15–1.24]). The excess number of hospitalizations in individuals with high and intermediate risk seemed to be attributable mainly to CVD. Individuals with higher genetic risk of CAD were more likely to be hospitalized due to cardiovascular causes (main diagnosis at discharge) than individuals with low genetic risk (Intermediate genetic risk: IRR 1.17 [95% CI 1.09–1.26], $p = 0.000032$; High genetic risk: IRR 1.31 [95% CI 1.20–1.43], $p = 5.17 \times 10^{-10}$). No association was found to hospitalization due to non CVD causes (data not shown).

Individuals in the highest quintile of the CAD_GRS_50 had an 18% increased risk of ever being hospitalized compared to individuals in the lowest quintile (High OR 1.18 [95% CI 1.07–1.30], $p = 0.001$).

3.2. Genetic CAD risk and total time spent hospitalized during follow-up

During follow-up, 522,493 days of hospitalization were consumed by 17,254 individuals with one or more hospitalizations. In the entire cohort, Individuals with high and intermediate genetic risk spent approximately 17% more and 10% more time being hospitalized, respectively, compared with individuals with low genetic risk (Table 2).

3.3. Genetic CAD risk in relation to risk of mortality during follow-up and sensitivity analyse

Individuals with high and intermediate genetic risk were approximately 16% and 9% more likely to die of any cause during the follow-

Table 2
The number of hospitalizations and days spent in hospital in individuals with high and intermediate GRS for CAD compared to individuals with low genetic risk.

	Number of hospitalizations				
	CAD-GRS50 Low (reference)	CAD-GRS50 Intermediate (IRR [95% CI])	*p*-value	CAD-GRS50 High (IRR [95% CI])	p-Value
Model 1	1.00	1.08 (1.03–1.13)	0.001	1.11 (1.05–1.18)	0.00018
Model 2	1.00	1.07 (1.02–1.12)	0.005	1.10 (1.04–1.16)	0.001
Survivors	1.00	1.08 (1.02–1.15)	0.012	1.11 (1.03–1.19)	0.004
	Number of hospitalization days				
	CAD-GRS50 Low (reference)	CAD-GRS50 Intermediate (IRR [95% CI])	p-value	CAD-GRS50 High (IRR [95% CI])	p-Value
Model 1	1.00	1.11 (1.04–1.18)	0.001	1.18 (1.10–1.28)	0.000010
Model 2	1.00	1.10 (1.04–1.17)	0.002	1.17 (1.08–1.26)	0.000050
Survivors	1.00	1.11 (1.01–1.22)	0.026	1.16 (1.04–1.28)	0.008

IRR = Incidence rate ratio.
Model 1: Negative binomial regression adjusted for age, sex and follow-up time.
Model 2: Negative binomial regression adjusted for age, sex, follow-up time, hypertension, prevalent diabetes, smoking, ApoA1 and ApoB.
Survivals: Negative binomial regression in individuals who were alive at the end of follow-up time, adjusted for age, sex, follow-up time, hypertension, prevalent diabetes, smoking, ApoA1 and ApoB.

up as compared to individuals with low genetic risk (Table 3). These individuals had highly increased risk of CVD mortality but, as expected, not the risk of mortality due to other causes (Table 3). In the multivariate analysis all included parameters were significantly associated with CVD mortality and all but the ApoB concentration were associated with all-cause mortality.

Since short follow-up time caused by premature mortality will decrease the likelihood of being hospitalized, we performed sensitivity analyses regarding genetic risk in relation to number of hospitalizations and total hospitalization time in individuals that were still alive at the end of follow-up. As compared to analyses including all individuals, these analyses gave similar results (Table 2).

4. Discussion

Our results show that individuals in the highest quintile of genetic risk for CAD have a 10% increased risk to be hospitalized when compared to individuals in the lowest genetic risk quintile, they spend more time in the hospital and are 30% more likely to be hospitalized for cardiovascular reasons.

To our knowledge this is the first study showing association between a genetic score for a common complex disease and hospitalization. We could also demonstrate that individuals from population based study with high genetic risk for CAD have higher all-cause mortality and this is driven largely by mortality due to cardiovascular causes. These individuals have not been selected on a prior higher risk of CAD and are drawn from general population, indicating that genetic screening could be beneficial even in non-selected individuals.

The genetic risk for an individual can be determined early in life and can therefore serve as guidance for the extent of intervention on individual bases. To prevent human suffering as well as reduce cost for society, prevention is always better than treatment of disease. Additional intervention studies are needed to establish whether individually adapted life style changes early in life and statin therapy, based on individual genetic risk, could prevent CAD and to what extent. Importantly, previous studies indicated that in mid-life, the polygenetic risk can be, if not eliminated, reduced to a large extent [6,7]. Apart from preventing CAD, we here provide evidence that such genotype guided life style and statin interventions have a potential to substantially reduce societal costs by reducing risk of hospitalization, number of hospitalizations and accumulated time spent hospitalized as well as potentially prolonging life by reducing mortality [7].

The GRS is a predictor of both CAD and hospitalizations independently of traditional risk factors [5]. The estimated risk is lower than for hypertension but it is in the same order of magnitude. Since hypertension is the biggest risk factor for premature mortality globally [15], interventions targeted at the 20% of the population with high genetic CAD risk have enormous potential given its commonness and large effect sizes on mortality and hospitalization risk [9].

There are several advantages benefitting our study. Both hospitalization data and the data on mortality have been collected from national registries that cover 100% of the population. This makes the data reliable as they do not rely on self-reporting. One could also argue that this study is performed in a double blind fashion as neither the patient nor the treating physician knew the genotype of the individual. Presence of traditional risk factors could lead to increased hospitalization based on the higher perceived risk by the doctor, however the genetic risk is absent from such bias.

The study was performed in middle aged population from Southern Sweden and studies in other ethnic populations and age groups are necessary to investigate the generalizability of our results. The genetic make-up of the Swedish populations is however similar to populations of European origin, making it plausible to extrapolate to other Caucasian population. Also the genetic predisposition of an individual to CAD is constant from birth and could be used as early prediction, follow-up of individuals from younger age would answer if GRS could be used in other age groups [12].

Our study population contains high male/female ratio (8973/14621) despite the fact that the invitations have been sent proportionally to men and women. Females were more likely to participate as is common in contemporary population based studies. As women have lower cardiovascular risk this introduces a healthy cohort bias into our study.

Despite the fact that the GRS for CAD consists of 50 SNPs, only a small part of the genetic variation is explained, limiting the interpretations of this study. It has been shown that GRS containing more genetic markers improves prediction and adding more SNPs might further increase the

Table 3
Total and CVD mortality according to GRS for CAD.

	CAD-GRS50 Low (reference)	CAD-GRS50 Intermediate (HR [95% CI])	p-value	CAD-GRS50 High (HR [95% CI])	p-Value
Total mortality	1.00	1.09 (1.02–1.16)	0.016	1.16 (1.07–1.25)	0.00038
CVD mortality	1.00	1.23 (1.08–1.39)	0.001	1.44 (1.25–1.66)	6.56×10^{-7}
Non CVD mortality	1.00	1.03 (0.95–1.12)	0.45	1.05 (0.95–1.15)	0.37

All analyses were performed by Cox regression and adjusted for age, sex, hypertension, prevalent diabetes, smoking, ApoA1 and ApoB.

strengths of our prediction. Also only common variation (Minor Allele Frequency [MAF] ≫ 0.05) is included in the GRS. Potential important information carried by rare variants is missing and this could weaken our results. It is also difficult to explore interactions and mechanisms by which these variants affect hospitalizations and there is need to elucidate these in further studies.

In conclusion, our results show that GRS for CAD can predict hospitalization and premature death mainly due to cardiovascular causes. This suggests that GRS can be used to early identify individuals and help to target individuals for early interventions to prevent disease, suffering, societal costs and to prolong life.

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Appendix A. Supplementary data

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