ESC European Society of Cardiology

European Heart Journal Open (2022) **2**, 1–10
https://doi.org/10.1093/ehjopen/oeac079

ORIGINAL ARTICLE
Epidemiology and prevention

Effectiveness and feasibility of cardiovascular disease personalized prevention on high polygenic risk score subjects: a randomized controlled pilot study

Margus Viigimaa [1,2,*†], Mikk Jürisson[3,†], Heti Pisarev[3], Ruth Kalda[3], Helene Alavere[4], Alar Irs[5], Aet Saar[2,6], Krista Fischer [4,7], Kristi Läll [4], Krista Kruuv-Käo[4], Nina Mars [8], Elisabeth Widen[8], Samuli Ripatti[8], and Andres Metspalu [4]

[1]Department of Health Technologies, Tallinn University of Technology, Ehitajate tee 5, 19086 Tallinn, Estonia; [2]Centre of Cardiology, North Estonia Medical Centre, Sütiste St. 19, 13419 Tallinn, Estonia; [3]Institute of Family Medicine and Public Health, University of Tartu, Ravila 19, 50411 Tartu, Estonia; [4]Institute of Genomics, University of Tartu, Riia 23b, 51010 Tartu, Estonia; [5]Heart Clinic, Tartu University Hospital, L. Puusepa 8, 50406 Tartu, Estonia; [6]Heart Clinic, University of Tartu, L. Puusepa 8, 50406 Tartu, Estonia; [7]Institute of Mathematics and Statistics, University of Tartu, Narva mnt 18, 51009 Tartu, Estonia; and [8]Institute for Molecular Medicine Finland, University of Helsinki, Tukholmankatu 8, 00014 Helsinki, Finland

Received 9 September 2022; revised 23 November 2022; accepted 13 December 2022; online publish-ahead-of-print 15 December 2022

Handling Editor: Magnus Bäck

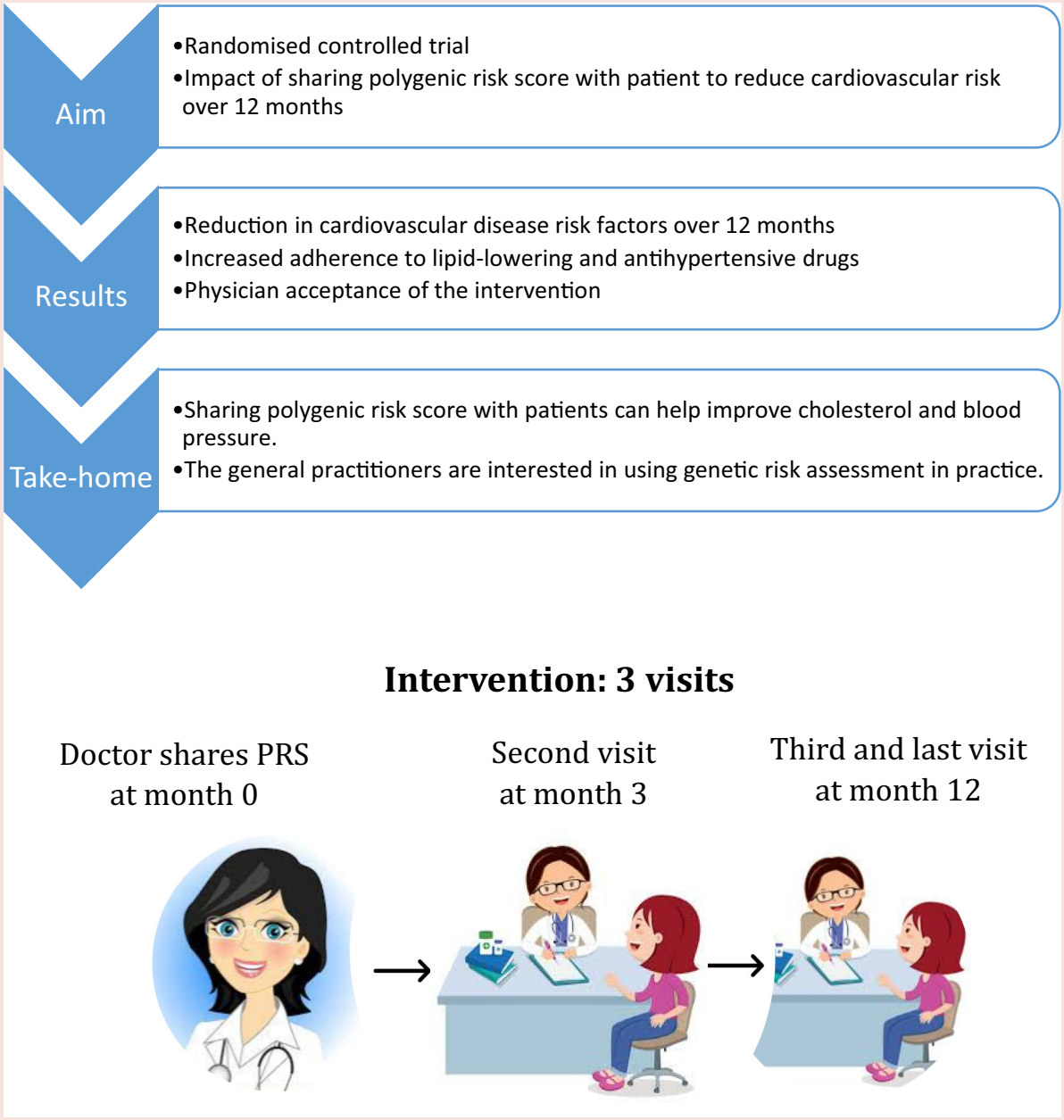
Aims The aim of this study was to evaluate the effect of the intervention by proactively sharing a patient's high polygenic risk score (PRS) for coronary artery disease (CAD). Outcomes included: (i) reduction in cardiovascular disease (CVD) risk factors over 12 months; (ii) difference in purchased prescriptions of lipid-lowering and anti-hypertensive drugs between intervention group and control group subjects; and (iii) opinion of the participating physicians and subjects on PRS usefulness.

Methods and results This randomized controlled trial was conducted among middle-aged subjects with a top 20% CAD PRS in a family medicine setting. Participants were selected from 26 953 Estonian Biobank cohort participants. Subjects were informed and counselled about their PRS score and CAD risk using the visual tool at baseline (Visit I), counselling session (Visit II), and on the final Visit III at 12 months. The primary endpoint was not significantly different. However, the intervention group participants had a significantly higher probability of initiating statin treatment compared with the controls. Their levels of LDL-cholesterol (LDL-C) were significantly decreased compared with baseline on Visit III and significantly lower than in the control group. The vast majority of participating family physicians believe that finding out about genetic risks will affect the subject's lifestyle and medication compliance.

Conclusion Most of our outcome measures were in favour of this intervention. Participants achieved larger changes in cholesterol and blood pressure values. The vast majority (98.4%) of family physicians are interested in continuing to use genetic risk assessment in practice.

* Corresponding author. Tel/fax: +372 6171415, Email: margus.viigimaa@regionaalhaigla.ee
† These authors are joint first authors.

Graphical Abstract



Keywords Polygenic risk score • coronary artery disease • personalized prevention

Introduction

Although prevention of cardiovascular disease (CVD) has long been a focus of public health and clinical medicine, the prevalence of CVD remains high. Estonia is a country with one of the highest CVD event rates in Europe and the prevalence of CVD risk factors is high.[1,2] For optimal management decisions in primary prevention, an accurate estimation of an individual's atherosclerotic CVD risk is needed. Several risk scores have been developed for guidance on whether and when to start preventive therapy. The European Society of Cardiology (ESC) suggests Systematic COronary Risk Estimation (SCORE) and recently SCORE2.[3–6] The SCORE general principle stresses the importance of estimating individuals' absolute risk for developing CVD and adjusting the intensity of preventive therapy accordingly. The predictive ability of SCORE for CVD risk prediction in the high-risk population of Estonia is at an acceptable level.[7]

However, SCORE does not currently include genetic risk factors. Polygenic risk scores (PRSs) have been shown to offer a powerful

new approach to measuring genetic risk for CVD and to enhance risk prediction.[8] Several publications[9,10] suggest that the current risk stratification algorithms would become more efficient if they were integrated with genetic risk assessment. There is consistent evidence from large-scale international studies that CVD is highly heritable and is influenced by a wide range of genetic factors. As confirmed by genome-wide association studies, there are more than 50 genetic loci across the whole genome that are associated with CVD. It has also been shown that including hundreds to thousands of single-nucleotide polymorphisms (SNPs) with less statistical confidence in addition to the SNPs with proven significance, can improve the actual risk predictions. By using large European cohorts, a study on CVD prediction demonstrated that integration of such a genetic risk score with the conventional non-genetic risk scores improved 10-year risk prediction.[11] It is now clear that CVD is a polygenic disease; therefore, an efficient genomic predictor should combine data across the large number of SNPs. There has been considerable progress in PRS optimization to generate a single score that could subsequently be used in individual risk stratification.[10,12–14]

An analysis conducted on the Estonian Biobank (EstBB) cohort (Estonian Genome Center database) indicated a considerably higher hazard for acute CVD events for individuals at high genetic risk, with the results being consistent with the study of Abraham *et al.*[11,12,15] According to SCORE criteria, close to 50% of men and 20% of women aged 40–70 would potentially need statin therapy to prevent acute CVD events; however, only 4% actually receive such therapy. At the same time, more than 50% of the cohort received a CVD diagnosis by the age of 75, and by this age, the probability of myocardial infarction is about 20% in males and 5% in females. Given the high cardiovascular mortality rate in Estonia, we could expect an even greater benefit in terms of prevented events as the result of the implementation of the personalized risk stratification algorithms.

Therefore, our primary aim was to assess the impact of a PRS intervention to reduce cardiovascular risk scores among patients in a primary care setting. Our main outcomes included: (i) compare changes in the 10-year overall CVD mortality scores between study groups 12 months after the start of the study as measured by the Kardiokompassi method; (ii) investigate the difference in purchased prescriptions of lipid-lowering and anti-hypertensive drugs between intervention group and control group subjects; and (iii) assess the opinions of the participating physicians and participants on their knowledge of polygenic risk and its usefulness in practice.

Methods

We have performed a randomized controlled trial (RCT) on CVD risk factor reduction among middle-aged subjects who are in the top 20% coronary artery disease (CAD) PRS. The 1st CAD risk algorithm for the Estonian population was created. The study was conducted in regular primary care settings throughout Estonia and incorporated 73 general practitioners. The intervention arm received an intake assessment, was provided with the PRS score together with initial counselling, and returned for a regular visit and counselling at Months 3 and 12 after intake. The control group received the same intervention on Visit I at the end of the study period.

Inclusion criteria for study participants

(1) Age 30–65 for males and 40–70 for females.
(2) Is in the top 20% CAD PRS.
(3) No current diagnosis of CAD (ICD-10 categories I20-I25), cerebrovascular disease (I60–64, I69, and G45), or peripheral vascular disease (I65–66, I67.2, I70, and I73.9).
(4) No current diagnosis of diabetes mellitus (E10–14).
(5) Is not currently receiving any cholesterol-lowering treatment (such as statin therapy).

The study flow chart is displayed in *Figure 1*.

The randomization was performed at the EstBB after the consent from a participant was received. The randomization was carried out in blocks of random size (average block size 100, range 88–118). The names of the intervention group subjects were extended to the participating family doctors right after the randomization was completed. The names of the subjects in the control group were not communicated to the family physicians at the beginning of the study period. The control group underwent only one visit (Visit I) at the end of the study period, where they gave consent, had a blood test and health parameter assessment, and were informed about their polygenic and combined risk of CAD. They also received counselling and treatment if necessary.

Subjects of the intervention group were actively invited to the family doctor's visit, the study was introduced, and they have given their informed consent to participate. Three study visits were made during the study: baseline, after 3 months, and after 12 months. At the 1st visit, the informed consent was signed, medical history and health data were collected. Polygenic CAD risk and the 10-year combined CAD risk were calculated using the Kardiokompassi method.[16] Patients were provided health counselling and preventive treatment as needed according to the guidelines.[3] Subjects' height, body weight, body mass index, waist circumference, systolic and diastolic blood pressure (SBP, DBP), cholesterol, LDL cholesterol (LDL-C), blood glucose, physical activity, and smoking status were studied at all three visits in the intervention group, and at the 12-month visit in the control group. The 2nd and 3rd visits assessed the change in aggregate risk, provided additional counselling, and asked for feedback of participants.

The names of the subjects in the control group were not communicated to the family physicians. During the follow-up period, patients in the control arm were treated based on regular primary care protocols according to current treatment guidelines (including opportunistic screening for CVD prevention in middle-aged people). Subjects in the control group underwent one visit to the family physician 12 months after the start of the study where they received the same intervention as intervention arm participants at the 1st visit. They gave consent to the study and had a blood test and health parameter assessment. Control group subjects were also informed about their polygenic and combined risk of CAD and health behaviours and received counselling. The participation rate was high both in the intervention group (95.9%) and in the control group (95.1%). In the intervention group compared with the control group, 17 and 13 subjects refused the PRS visit, respectively, and 4 and 12 subjects did not respond to the family doctor's invitation.

The age and sex distribution of the study cohort are given in *Table 1*.

In this nationwide study, participants were selected from 26 953 EstBB cohort participants (10 042 men and 16 911 women). Subjects with the highest PRS quintile for CAD (1017 women and 712 men) were invited to the study. Of these, 589 subjects responded to the first e-mail and 429 to the second, giving an overall response rate of 59%. Thus, we enrolled a total of 1018 persons; 507 subjects were randomized to the intervention group and 511 to the control group.

The average age of study participants was 51.2 ± 9.8 years old at the time of enrolment (SD). Of a total of 1018 subjects, 62% were women and 38% were men. The mean follow-up period was 405 days (316–577 days), with a median of 401 days. The study groups did not differ significantly in terms of gender or age distribution (gender $P = 0.65$, age $P = 0.623$).

Cardiovascular risk assessment and management

The study used Kardiokompassi as an interactive web-based tool for patients and physicians to manage and use genomic information for the prevention of CAD. Kardiokompassi is an instrument for primary prevention and has been developed by the Institute for Molecular Medicine Finland, University of Helsinki.[16] This tool comprehensively utilizes the genetic profile of an individual in combination with conventional health information to assess the risk for CAD. The risk assessments obtained with this instrument are based on traditional health data as well as a genetic risk score containing 49 000 DNA variants associated with CAD. A secure website was created in this study for the use of the Kardiokompassi during the study by both family doctors and patients. This web app takes an individualized approach to support health behaviour changes. The calculator evaluates and

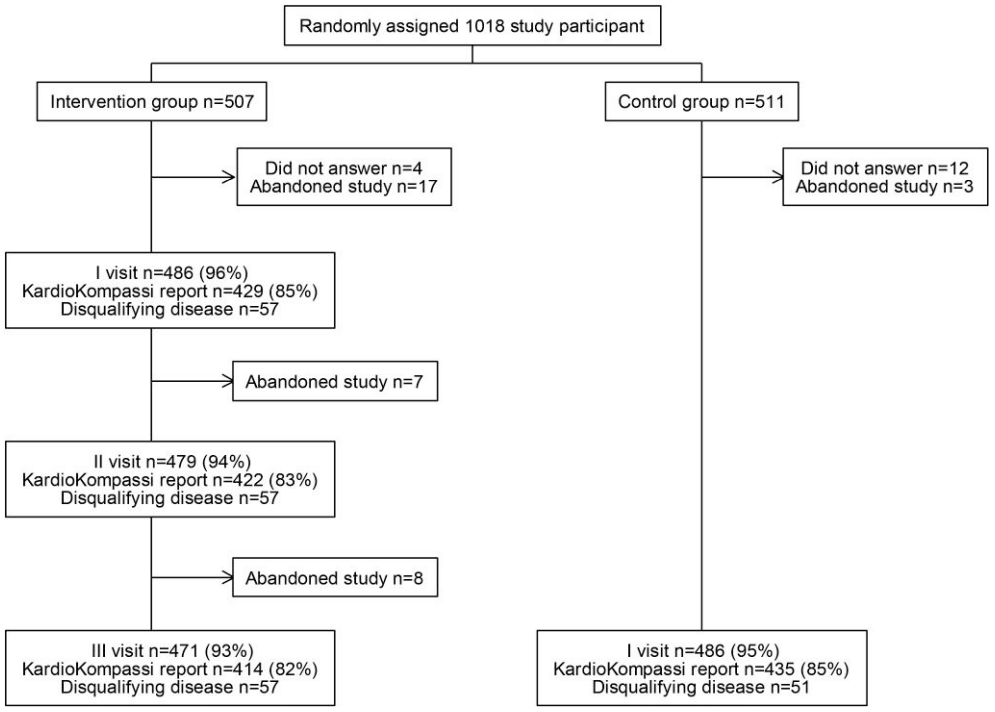


Figure 1 Study flow chart.

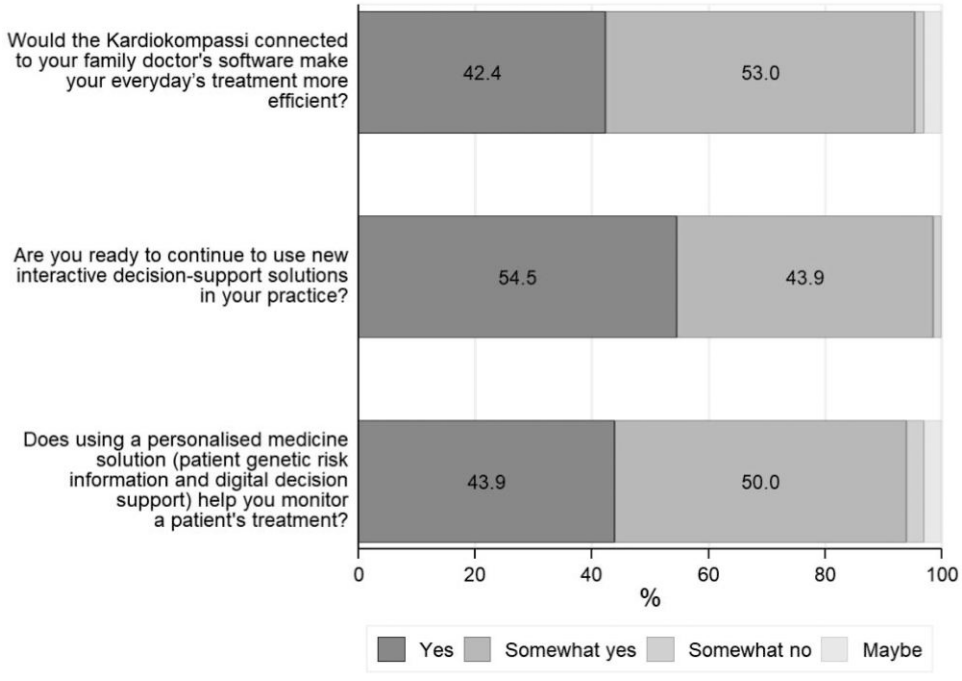


Figure 2 Responses to the physician feedback questionnaire.

Table 1 Age and sex distribution of the study cohort

	Intervention group		Control group	
	n	Age (years) Mean (SD)	*n*	Age (years) Mean (SD)
Male	188	46.6 (10.2)	197	46.7 (10.3)
Female	319	53.8 (8.4)	314	54.3 (8.5)

interprets personal risk for developing CAD during the next 10 years. Using the interactive interface, users can also test how different lifestyle changes, such as quitting smoking, impact their risk. All investigators in the study received training in the use of the Kardiokompassi before the start of the study.

Subjects received focused management based on the ESC guidelines.[3] Detailed intervention instructions were created for participating general practitioners and three special training sessions were provided, including risk assessment, lifestyle counselling (smoking cessation, physical activity, diet, body weight), dyslipidaemia (diagnosis, indications for statin treatment, drug selection, monitoring), and treatment of hypertension (diagnosis, treatment). Data about purchased prescriptions (ATC: C03*, C07*, C08*, C09*, C10*) were retrieved from the Estonian Health Insurance Fund.

The study used web-based REDCap (Research Electronic Data Capture) software to create and manage data. Each general practitioner was only granted access to the patient's data on his or her list in order to ensure the protection of personal data. Almost all data collected during the study were entered directly into REDCap. A paper file contained only the informed consent of the subjects; this file was stored in a locked cabinet only accessible by the principal investigator.

Study monitoring and quality assurance

Study monitoring was performed by the monitor of the Clinical Research Center of the University of Tartu throughout the study period between April 2019 and December 2020. The monitor checked the quality and completeness of the data entered into REDCap twice a month for the two subjects in each study centre, based on the study quality control plan. In addition, during the initial period of the study, the monitor conducted an on-site inspection in one urban and one rural general practitioner's practice. The monitor submitted monthly reports outlining the shortcomings identified. The monitoring summaries helped to guide the researchers and thus ensure the quality of the survey data collection. During the study, information letters were regularly sent to the researchers, giving an overview of the progress of the project. Support was also provided throughout the period to address both the involvement and counselling of subjects and information technology issues.

This study was approved by the Research Ethics Committee of the University of Tartu on 21 May 2018 under protocol No 282/T-28. Participants have provided written informed consent. The clinical trial was registered in the trial database ClinicalTrials.gov entitled 'Proactive Cardiovascular Prevention Strategy in Subjects With High Genetic Risk' (EstPerMedCV, designation NCT04291157).

Statistical analyses

Frequencies and percentages are given for categorical background characteristics. Continuous background characteristics and clinical measurements are described using means and standard deviations. In addition, the median and range are presented for the risk scores. A paired *t*-test (for normally distributed variables) or non-parametric Wilcoxon sign test (for non-normally distributed variables) was used for statistical comparison between measurements on Visit I vs. II and Visits I vs. III; a comparison between the intervention group and the control group was performed using Student's *t*-test or the Mann–Whitney *U* test. Bonferroni correction was used to correct multiple testing errors on *P*-values and confidence intervals. Differences between groups are presented with the mean and 95% confidence intervals. The Fisher's exact test was used to compare the number of persons who purchased prescriptions. The number of prescriptions purchased per follow-up year is compared with Poisson regression adjusted to age, sex, PRS, and prescriptions purchased before follow-up, IRR (incidence rate ratio), and 95% confidence are presented. *P*-values <0.05 are considered statistically significant. Analysis has been performed using the statistical software Stata14.2.

Results

Each participant's family history of CVD was investigated using interviews, and retrieving register-based information. Arterial hypertension occurred in 71% of the families of the subjects, stroke was present in 38%, CAD in 48%, diabetes in 33%, and CVD at an early age in 37% of the subjects' families. The distribution of these diseases was similar in the families of both study groups.

The main health parameters of study participants are displayed in *Table 2*. The comparison between the intervention group (I, II, and III visits) and the control group is also provided showing statistically significant ($P < 0.05$) differences over time and/or between groups. The primary endpoint was not significantly different. However, the intervention group participants had significantly higher probability of initiating statin treatment compared with controls.

The mean SBP in intervention group subjects on Visit I was 129 mmHg and was significantly ($P < 0.001$) decreased on Visit II by 2.5 mmHg. However, on Visit III, the mean SBP has returned to 129 mmHg level, which did not differ statistically significantly from the control group (130 mmHg).

Total cholesterol levels were significantly decreased by 0.16 mmol/L ($P < 0.006$) in intervention group subjects on Visit II. When comparing the intervention vs. control group, the mean cholesterol value on Visit III (5.4 mmol/L) was 0.23 mmol/L lower ($P < 0.004$) in the intervention group. The mean intervention group LDL-C level on the baseline was 3.6 mmol/L and decreased significantly on Visits II and III by 0.17 mmol/L ($P < 0.004$) and 0.12 mmol/L ($P < 0.023$), accordingly. When comparing Visit III LDL-C mean values between study groups, the control group's mean LDL-C value was 0.19 mmol/L higher ($P < 0.01$) compared with the intervention group.

Physical activity at baseline in the intervention group was 454.3 min/week. By Visit III, physical activity had increased by 97.9 min/week ($P < 0.001$) compared with baseline. Controls had significantly higher physical activity (630.7 min/week) than the intervention group. Cigarette smoking was quite common among study participants (21.8% in the intervention group and 21.6% in the control group). The number of smokers decreased in the intervention group by 2.3% on Visit II and by 2.8% on Visit III. However, this change was not statistically significant.

Polygenic risk score and the 10-year cumulative risk of cardiovascular disease death by the Kardiokompassi method

In the intervention group mean PRS was 1.41 and in the control group 1.42. The 10-year cumulative risk of CVD death, including PRS, was 2.63%±3.95 in the study group at the 1st visit and increased to 2.82%±4.09 on Visit III that was caused by the increased age of the subjects. The 10-year cumulative risk of CVD death in the control group was 3.15 ± 4.15, statistically indistinguishable from the intervention group. Thus, there were no statistically significant differences in the study's primary endpoints between study groups. *Table 3* demonstrates the 10-year cumulative risk of CVD death, taking into account only traditional risk factors and the Kardiokompassi method.

Purchased anti-hypertensive (C03–C09) and lipid-lowering (C10) prescriptions before the study were similar among the intervention and control groups (*Table 4*). During the follow-up time, significantly

Table 2 Characteristics of intervention and control group subjects

	Intervention group			Control group	Difference (95% CI)		
	I visit *n* = 486 (96%) Mean (SD)	II visit *n* = 479 (94%) Mean (SD)	III visit *n* = 471 (93%) Mean (SD)	*n* = 486 (95%) Mean (SD)	II vs. I	III vs. I	III vs. control
Age (years)	51.4 (9.7)	51.8 (9.7)	52.6 (9.7)	52.9 (9.8)			−0.28 (−1.8–1.23)
Height (cm)	169.9 (9.5)	169.9 (9.5)	169.8 (9.6)	170.1 (9.5)			−0.25 (−1.73–1.23)
Weight (kg)	82.4 (18)	82.3 (17.9)	82.6 (18.1)	82.2 (18.6)	−0.24 (−0.55–0.07)	0.03 (−0.45–0.51)	0.44 (−2.41–3.28)
BMI (kg/m^2)	28.5 (5.6)	28.4 (5.6)	28.6 (5.6)	28.3 (5.6)	−0.08 (−0.19–0.02)	0.03 (−0.14–0.19)	0.28 (−0.59–1.15)
Waist circumference (cm)	94.7 (14.7)	94.1 (14.6)	94.3 (15.1)	93.3 (15.1)	−0.72* (−1.19– −0.26)	−0.51 (−1.16–0.13)	1.06 (−1.28–3.41)
SBP (mmHg)	129.4 (17.2)	126.9 (15)	128.5 (15.8)	130.2 (15.9)	−2.69** (−4.2– −1.19)	−1.06 (−2.81–0.69)	−1.73 (−4.18–0.72)
DBP (mmHg)	81.1 (10.3)	80.2 (10)	80.2 (10)	81.4 (10.1)	−0.96 (−1.99–0.08)	−0.92*** (−1.95–0.11)	−1.22 (−2.78–0.34)
Cholesterol (mmol/L)	5.5 (1.1)	5.3 (1)	5.4 (1.1)	5.7 (1.1)	−0.16** (−0.27– −0.05)	−0.03 (−0.13–0.06)	−0.23* (−0.40– −0.06)
LDL-C (mmol/L)	3.6 (1)	3.4 (1)	3.4 (1.1)	3.6 (1.1)	−0.18** (−0.28– −0.07)	−0.12**** (0.23–0.01)	−0.20* (−0.36– −0.03)
Glucose (mmol/L)	5.3 (1)	5.4 (1)	5.4 (1)	5.4 (0.9)	0.02 (−0.07–0.12)	0.09**** (0.01–0.17)	−0.01 (−0.15–0.13)
Physical activity (min/week)	454.3 (612.6)	503.3 (613.1)	552.2 (639.5)	630.7 (742.3)	55**** (1.1–109)	104** (47–162)	−78 (−186–29)
Smoking (%)	21.6	19.2	18.5	21.8	−2.3*** (−4.7–0.08)	−2.8*** (−5.8–0.3)	−3.3 (−9.5–2.9)

LDL-C, LDL cholesterol.
*$P < 0.01$, **$P < 0.001$, ***$P < 0.1$, ****$P < 0.05$.

Table 3 Ten-year cumulative absolute risk of cardiovascular disease death by traditional risk factors (cholesterol, systolic blood pressure, age, sex, and smoking) and by the Kardiokompassi method

	INTERVENTION GROUP						CONTROL GROUP		INTERVENTION GROUP VISIT III VS. CONTROL GROUP
	I VISIT *N* = 429 (85%)		II VISIT *N* = 422 (83%)		III VISIT *N* = 414 (82%)		*N* = 435 (85%)		
	MEAN (SD)	MEDIAN (MIN–MAX)	MEAN (SD)	MEDIAN (MIN–MAX)	MEAN (SD)	MEDIAN (MIN–MAX)	MEAN (SD)	MEDIAN (MIN–MAX)	*P*-VALUE
Risk of CVD death, accounting for traditional risk factors	2.31 (3.48)	0.80 (0.04–24.9)	2.28 (3.53)	0.83 (0.04–24.9)	2.48 (3.62)	0.91 (0.05–32.1)	2.76 (3.70)	1.06 (0.06–31.4)	0.16
Risk of CVD death, accounting for traditional and polygenic risk	2.63 (3.95)	0.95 (0.05–27.3)	2.59 (3.98)	0.95 (0.05–28.5)	2.82 (4.09)	1.1 (0.06–35.1)	3.15 (4.19)	1.2 (0.1–35.2)	0.15

CVD, cardiovascular disease.

Table 4 Purchased prescriptions of lipid-lowering and anti-hypertensive drugs in intervention

	Intervention group ($n = 507$)		Control group ($n = 511$)		Comparison	
	Persons purchased prescription *n* (%)	No. of purchased prescriptions per person-year	Persons purchased prescription *n* (%)	No. of purchased prescriptions per person-year	No. of persons (*P*-value)	IRR[a] (95% CI) for no. of prescription
ATC: C03*-C09*						
Before follow-up begins	129 (25.4)	0.58 (0.52–0.65)	137 (26.8)	0.92 (0.84–1.01)	0.669	
Since 1st visit to last visit/ controls: 1 year before visit	188 (37.1)	2.54 (2.41–2.69)	158 (30.9)	2.17 (2.05–2.30)	0.04	1.38 (1.27–1.50) $P < 0.001$
ATC: C10*						
Before follow-up begins	40 (7.8)	0.12 (0.09–0.15)	47 (9.2)	0.19 (0.15–0.23)	0.502	
Since 1st visit to last visit/ controls: 1 year before visit	110 (21.7)	0.98 (0.89–1.07)	59 (11.5)	0.48 (0.42–0.54)	<0.001	2.48 (2.12–2.90) $P < 0.001$

IRR, incidence rate ratio; PRS, polygenic risk score.
[a]Adjusted for age, sex, PRS, and number of prescriptions before follow-up.

more intervention group subjects purchased prescriptions compared with the control group (C03–C09: 37.1% vs. 30.9%, $P = 0.04$; C10: 21.7 vs. 11.5, $P < 0.001$). The number of prescriptions per follow-up year was 1.38 [95% confidence interval (CI) 1.27–1.5] times higher for anti-hypertensive drugs and 2.48 (95% CI 2.12–2.90) times higher for the lipid-lowering medication in the intervention group compared with the control group. Intervention group subjects achieved larger changes in cholesterol and blood pressure values.

The study also evaluated the opinions of the participating subjects and their physicians about their knowledge of polygenic risk and its usefulness via feedback questionnaires. The majority of study subjects have reported that knowing the genetic risk helps improve lifestyle and medication compliance. The vast majority of participants have recognized lifestyle as a major factor in CVD risk and more than half of participants were convinced that genetics is very important as well. The average consultation time by doctors was 29 min. More than 90% of participants rated the information and explanations given during the counselling session as sufficient. The vast majority of participating general practitioners believe that finding out about genetic risks will affect the subject's lifestyle and medication compliance. The vast majority (98.4%) of general practitioners were interested in continuing to use genetic risk assessment and counselling in their practice (*Figure 2*).

Discussion

Our study has demonstrated that the intervention group participants had a significantly higher probability of initiating statin treatment compared with controls. Their levels of LDL-C were significantly decreased compared with baseline on Visit III by 0.12 mmol/L ($P < 0.023$) and significantly lower than the control group ($P < 0.01$) by 0.19 mmol/L. The vast majority of participating family physicians believe that finding out about genetic risks will affect the subject's lifestyle and medication compliance and they are interested in continuing to use genetic risk assessment in practice.

The literature in the area of PRS for CAD reveals that although there is great potential, this strategy remains underdeveloped.[9,17,18] One reason may be that the implications of stratification for clinical practice have not yet been fully investigated. There is currently no solid evidence for the clinical utility of PRS for CVD prevention, and this was the motivation for our study. To our knowledge, this is the 1st RCT to evaluate a CVD risk factor intervention in middle-aged subjects with very high CVD PRSs. We aimed to assess the impact on CVD risk factors over 12 months and evaluate the difference in the 10-year overall CVD mortality scores between study groups 12 months after the start of the study as measured by the Kardiokompassi method.

The role of polygenic risk score for coronary artery disease in risk prediction

The incremental value of PRS in addition to traditional risk prediction models for CAD is not clear. A recent retrospective cohort study of the predictive accuracy of a previously validated PRS was published.[19] In this analysis of two cohorts of US adults, the PRS was associated with incident coronary heart disease events but did not significantly improve risk reclassification compared with conventional predictors. Another recent publication has demonstrated that the addition of a PRS for CAD to pooled cohort equations was associated with a statistically significant but modest improvement in the predictive accuracy for incident CAD and improved risk stratification for only a small proportion of individuals.[20]

There has been constructive opposition to these articles. On the one hand, it is considered that even a small improvement in risk prediction using the PRS has clinical significance. On the other hand, the main problem in these studies have enrolled relatively older (>60 years)

populations. In our study (~47- and 54-year old for males and females, respectively), the study group subjects had a mean PRS of 1.41 and a control group of 1.42 that indicates a substantial CAD risk increase among these subjects (*Table 2*). The main advantage of the PRS is that it predicts risk significantly earlier than traditional risk factors. Polygenic risk score can be diagnosed at birth and remains stable throughout life. Thus, CAD risk SNPs are detectable in younger individuals before traditional, clinically apparent risk factors are present, such as hypertension or elevated lipids.[19,20] In addition, lifestyle and environmental factors have been shown to be independent of and complementary to genetic risk. Because PRS can be quantified from a young age, it can provide information to mitigate the elevated lifetime risk that even moderate LDL-C exposure causes in individuals with a high CAD PRS.[21,22] We believe that proactive, early identification and communication with patients allows them to modify habits at a younger age, thus accruing more years of benefits, or at least slowing down the accumulation of excess risk.

A recent study by Helsinki University investigators has shown that high PRS contributed 21–38% higher lifetime risk, and 4–9 years earlier disease onset.[23] According to the UK Biobank study, people with the highest PRS of 5% are about three times more likely to have coronary heart disease.[24] This elevated risk is equivalent to the risk of coronary heart disease in patients with familial hypercholesterolaemia. Another recent study investigating the British Biobank's young myocardial infarction patients found that 1.7% had a familial hypercholesterolaemia mutation and as many as 17% had an extremely high PRS.[25] An integrated risk tool combining a current clinical risk tool and a PRS has been successfully validated also across multiple ethnicities and ancestries.[8]

In the secondary prevention of CAD, the incidence of major adverse cardiac events was strongly related to PRS and this PRS relationship was not explained by baseline LDL-C or other established risk factors.[26] An additional 4.1% of primary prevention patients may be recommended for statin therapy if high CAD PRS were considered a guideline-based risk-enhancing factor.[27] Thus, the involvement of the PRS in CAD prevention is of great significance and potential.

Impact of a proactive high polygenic risk score-based prevention strategy on cardiovascular disease risk factors

There is currently only very limited evidence for the high PRS-based proactive prevention effect on CVD risk reduction.[28] Risk captured by PRS appears largely independent of traditional risk factors and can be identified prior to the development of traditional clinical risk factors. The potential benefits of PRSs include cost-effective enhancement of primary disease prevention, more refined diagnoses, and improved precision when prescribing medicines.[29] Genetic risk is modifiable through lifestyle modifications and medications. However, further work is needed before PRS can be implemented clinically.[30] Nevertheless, recent efforts have begun to demonstrate evidence supporting the personal and clinical utility of polygenic risk profiling.[18]

In the intervention group, we described improvement in many health indicators and risk scores at Visit II, with many indicators having improved, such as waist circumference, SBP, cholesterol levels, physical activity, and smoking prevalence. This is in line with a recent paper showing that web-based communication of personal atherosclerotic CVD risk data including polygenic risk to middle-aged persons motivates positive changes in health behaviour.[17] Another paper has revealed the role of CHD risk estimates that incorporated genetic risk information in lowering of LDL-C levels compared with CHD risk based on conventional risk factors alone.[31] However, one study in participants with at least moderate risk of CAD has demonstrated that adding PRS to standard-of-care did not change lipids, adherence, or psychological outcomes.[32] By the 3rd visit, however, the improvements had regressed with only the differences in LDL-C levels, total cholesterol, physical activity, and smoking prevalence remaining statistically significant. One modification to sustain momentum could be an additional visit or contact at Months 6 and 9 to intensify a healthy lifestyle. Another major reason to explain the diminished effect on SBP was the Covid-19 pandemic, which has delayed the time interval between Visits II and III. In the Covid-19 pandemic, the cardiovascular risk may have been considered by study participants to be of secondary importance, and lockdown measures may have impeded lifestyle changes.

In the present randomized study, knowledge of the high polygenic risk of CVD with concomitant lifestyle counselling and treatment achieved larger and more permanent changes in health indicators than could have been achieved by medication alone (LDL-C and blood pressure values) while smaller changes in lifestyle indicators were sustained. These findings suggest that while lifestyle-related health indicators can be improved in the short term (3 months), these changes are difficult to sustain over the long term (1 year). However, the observation period was short and longer-term intervention studies are needed to draw definitive conclusions. Perhaps most importantly, the vast majority (98.4%) of general practitioners were interested in continuing to use genetic risk assessment in their practice.

A high polygenic risk score for coronary artery disease is associated with 3 × risk reduction on lipid-lowering therapy

People with the highest burden of genetic risk derived the largest relative and absolute clinical benefit from statin therapy. In a large study, the number needed to treat to prevent a cardiac event was found to be an impressive three times lower among those with high genetic risk compared with low.[33] Integration of the PRS in the risk stratification algorithms would lead to more accurate identification of those in need of statin therapy to prevent CVD events.

Similar observations have been made by two recent proprotein convertase subtilisin/kexin type 9 inhibitors trials (FOURIER and ODYSSEY OUTCOMES). Patients with high genetic risk, regardless of clinical risk, had a high event rate, and derived the greatest relative and absolute benefit from evolocumab.[34] A high PRS for CAD is associated with elevated risk for recurrent MACE after acute coronary syndrome and a larger absolute and relative risk reduction with alirocumab treatment.[26] These results substantiate that PRS provides a useful independent tool for risk stratification and precision medicine.

Limitations

The study was performed during a period of the Covid-19 pandemic when the health priorities of the subjects have responded to shifting public health guidance and less attention was paid to cardiovascular risk modification. There is a lack of a rigid evaluation on medication adherence. Some baseline data for the control group were not available for analysis and controls had higher physical activity than the intervention group. However, the age and sex distribution were comparable in both study groups inferring that the randomized groups were comparable in major variables. A quality-of-life questionnaire has not been used in the assessment of interest of general practitioners in continuing to use genetic risk assessment.

Conclusions

Most of our outcome measures were in favour of this intervention and some (LDL-C, SBP, and smoking cessation) demonstrated durable improvement. Participants achieved larger changes in cholesterol and blood pressure values and smaller changes in lifestyle indicators. The intervention group participants started to use statins more often.

Their levels of LDL-C were significantly decreased compared with baseline and significantly lower than in the control group. The vast majority of participating general practitioners believe that finding out about genetic risks will affect the subject's lifestyle and medication compliance and are interested in continuing to use genetic risk assessment in practice.

Lead author biography

Prof. Margus Viigimaa is the Research Chief of the Centre of Cardiology, North Estonia Medical Centre and Head of the Centre for Cardiovascular Medicine, Tallinn University of Technology. He has published more than 300 original scientific papers, H-index is 43, and the number of citations is 36 135 (Scopus database). He is the President of the Baltic Atherosclerosis Society, a Fellow of the American College of Cardiology, a Fellow of the European Society of Cardiology, and past Council member of the European Society of Hypertension. He is an honorary member of the Swedish Society of Hypertension, Hungarian Society of Hypertension, and Bulgarian Hypertension League.

Author contributions

M.V. and M.J. contributed equally to the manuscript. All contributed to the conception and design of the work, acquisition, analysis, and interpretation of data for the work. M.V. and M.J. drafted the manuscript. All critically revised the manuscript. All authors gave final approval.

Acknowledgements

The authors recognize the contributions of the study participants and their general practitioners, without whom we would not have been able to contribute these findings. They also wish to acknowledge the Estonian Genome Center and finally, they recognize the thoughtful editorial contributions of Allison Krug, MPH.

Funding

The research has been funded by the 'Strengthening of sectorial R&D (RITA)' activity 1 'Support for strategic R&D activities.'

Conflict of interest: None declared.

Data availability

No new data were generated in support of the article.

References

1. Timmis A, Townsend N, Gale CP, Torbica A, Lettino M, Petersen SE, Mossialos EA, Maggioni AP, Kazakiewicz D, May HT, De Smedt D, Flather M, Zuhlke L, Beltrame JF, Huculeci R, Tavazzi L, Hindricks G, Bax J, Casadei B, Achenbach S, Wright L, Vardas P; European Society of Cardiology. European Society of Cardiology: cardiovascular disease statistics 2019. *Eur Heart J* 2020;**41**:12–85.
2. Kaldmäe M, Zemtsovskaja G, Abina J, Land T, Viigimaa M. Prevalence of cardiovascular disease risk factors in Tallinn, Estonia. *Medicina (B Aires)* 2017;**53**:268–276.
3. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney M-T, Corrà U, Cosyns B, Deaton C, Graham I, Hall MS, Hobbs FDR, Løchen M-L, Löllgen H, Marques-Vidal P, Perk J, Prescott E, Redon J, Richter DJ, Sattar N, Smulders Y, Tiberi M, van der Worp HB, van Dis I, Verschuren WM, Binno S; ESC Scientific Document Group. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 2016;**37**:2315–2381.
4. Conroy RM, Pyörälä K, Fitzgerald AP, Sans S, Menotti A, De Backer G, De Bacquer D, Ducimetière P, Jousilahti P, Keil U, Njølstad I, Oganov RG, Thomsen T, Tunstall-Pedoe H, Tverdal A, Wedel H, Whincup P, Wilhelmsen L, Graham IM; SCORE project group. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *Eur Heart J* 2003;**24**:987–1003.
5. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, Chapman MJ, De Backer GG, Delgado V, Ference BA, Graham IM, Halliday A, Landmesser U, Mihaylova B, Pedersen TR, Riccardi G, Richter DJ, Sabatine MS, Taskinen M-R, Tokgozoglu L, Wiklund O; ESC Scientific Document Group. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: the task force for the management of dyslipidaemias of the European Society of Cardiology and European Atherosclerosis Society. *Eur Heart J* 2020;**41**:111–188.
6. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, Benetos A, Biffi A, Boavida J-M, Capodanno D, Cosyns B, Crawford C, Davos CH, Desormais I, Di Angelantonio E, Franco OH, Halvorsen S, Hobbs FDR, Hollander M, Jankowska EA, Michal M, Sacco S, Sattar N, Tokgozoglu L, Tonstad S, Tsioufis KP, van Dis I, van Gelder IC, Wanner C, Williams B; ESC National Cardiac Societies; ESC Scientific Document Group. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J* 2021;**42**:3227–3337.
7. Saar A, Läll K, Alver M, Marandi T, Ainla T, Eha J, Metspalu A, Fischer K. Estimating the performance of three cardiovascular disease risk scores: the Estonian Biobank cohort study. *J Epidemiol Community Health* 2019;**73**:272–277.
8. Weale ME, Riveros-Mckay F, Selzam S, Seth P, Moore R, Tarran WA, Gradovich E, Giner-Delgado C, Palmer D, Wells D, Saffari A, Sivley RM, Lachapelle AS, Wand H, Clarke SL, Knowles JW, O'Sullivan JW, Ashley EA, McVean G, Plagnol V, Donnelly P. Validation of an integrated risk tool, including polygenic risk score, for atherosclerotic cardiovascular disease in multiple ethnicities and ancestries. *Am J Cardiol* 2021;**14**:e003304.
9. Rotter JI, Lin HJ. An outbreak of polygenic scores for coronary artery disease. *J Am Coll Cardiol* 2020;**75**:2781–2784.
10. Inouye M, Abraham G, Nelson CP, Wood AM, Sweeting MJ, Dudbridge F, Lai FY, Kaptoge S, Brozynska M, Wang T, Ye S, Webb TR, Rutter MK, Tzoulaki I, Patel RS, Loos RJF, Keavney B, Hemingway H, Thompson J, Watkins H, Deloukas P, Di Angelantonio E, Butterworth AS, Danesh J, Samani NJ. Genomic risk prediction of coronary artery disease in 480,000 adults: implications for primary prevention. *J Am Coll Cardiol* 2018;**72**:1883–1893.
11. Abraham G, Havulinna AS, Bhalala OG, Byars SG, De Livera AM, Yetukuri L, Tikkanen E, Perola M, Schunkert H, Sijbrands EJ, Palotie A, Samani NJ, Salomaa V, Ripatti S, Inouye M. Genomic prediction of coronary heart disease. *Eur Heart J* 2016;**37**:3267–3278.
12. Läll K, Mägi R, Morris A, Metspalu A, Fischer K. Personalized risk prediction for type 2 diabetes: the potential of genetic risk scores. *Genet Med* 2017;**19**:322–329.
13. Riveros-Mckay F, Weale ME, Moore R, Selzam S, Krapohl E, Sivley RM, Tarran WA, Sørensen P, Lachapelle AS, Griffiths JA, Saffari A, Deanfield J, Spencer CCA, Hippisley-Cox J, Hunter DJ, O'Sullivan JW, Ashley EA, Plagnol V, Donnelly P. Integrated polygenic tool substantially enhances coronary artery disease prediction. *Circ Genom Precis Med* 2021;**14**:e003304.
14. Thompson DJ, Wells D, Selzam S, Peneva I, Moore R, Sharp K, Tarran WA, Beard EJ, Riveros-Mckay F, Giner-Delgado C, Palmer D, Seth P, Harrison J, Futema M, Genomics England Research Consortium, McVean G, Plagnol V, Donnelly P, Weale ME. UK Biobank release and systematic evaluation of optimised polygenic risk scores for 53 diseases and quantitative traits. medRxiv preprint. doi:10.1101/2022.06.16.22276246.
15. Leitsalu L, Haller T, Esko T, Tammesoo M-L, Alavere H, Snieder H, Perola M, Ng PC, Mägi R, Milani L, Fischer K, Metspalu A. Cohort profile: Estonian Biobank of the Estonian Genome Center, University of Tartu. *Int J Epidemiol* 2015;**44**:1137–1147.
16. Widén E, Junna N, Ruotsalainen S, Surakka I, Mars N, Ripatti P, Partanen JJ, Aro J, Mustonen P, Tuomi T, Palotie A, Salomaa V, Kaprio J, Partanen J, Hotakainen K, Pöllänen P, Ripatti S. How communicating polygenic and clinical risk for atherosclerotic cardiovascular disease impacts health behavior: an observational follow-up study. *Circ Genom Precis Med* 2022;**15**:e003459.
17. Lloyd-Jones DM. Cardiovascular risk prediction: basic concepts, current status, and future directions. *Circulation* 2010;**121**:1768–1777.
18. Torkamani A, Wineinger NE, Topol EJ. The personal and clinical utility of polygenic risk scores. *Nat Rev Genet* 2018;**19**:581–590.
19. Mosley J, Gupta D, Tan J, Yao J, Wells QS, Shaffer CM, Kundu S, Robinson-Cohen C, Psaty BM, Rich SS, Post WS, Guo X, Rotter JI, Roden DM, Gerszten RE, Wang TJ. Predictive accuracy of a polygenic risk score compared with a clinical risk score for incident coronary heart disease. *JAMA* 2020;**323**:627–635.
20. Elliott J, Bodinier B, Bond TA, Chadeau-Hyam M, Evangelou E, Moons KGM, Dehghan A, Muller DC, Elliott P, Tzoulaki I. Predictive accuracy of a polygenic risk score—enhanced prediction model vs a clinical risk score for coronary artery disease. *JAMA* 2020;**323**:636–645.

21. Bolli A, Di Domenico P, Pastorino R, Busby GB, Bottà G. Risk of coronary artery disease conferred by low-density lipoprotein cholesterol depends on polygenic background. *Circulation* 2021;**143**:1452–1454.
22. Moorthie S, de Villiers CB, Brigden T, *et al.* Polygenic scores, risk and cardiovascular disease. Cambridge University; 2009. doi:10.1007/s11883-021-00915-6.
23. Mars N, Koskela JT, Ripatti P, Kiiskinen TTJ, Havulinna AS, Lindbohm JV, Ahola-Olli A, Kurki M, Karjalainen J, Palta P, Neale BM, Daly M, Salomaa V, Palotie A, Widén E, Ripatti S. Polygenic and clinical risk scores and their impact on age at onset and prediction of cardiometabolic diseases and common cancers. *Nat Med* 2020;**26**:549–557.
24. Khera AV, Chaffin M, Aragam KG, Haas ME, Roselli C, Choi SH, Natarajan P, Lander ES, Lubitz SA, Ellinor PT, Kathiresan S. Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. *Nat Genet* 2018;**50**:1219–1224.
25. Thériault S, Lali R, Chong M, Velianou JL, Natarajan MK, Paré G. Polygenic contribution in individuals with early-onset coronary artery disease. *Circ Genom Precis Med* 2018;**11**: e001849.
26. Damask A, Steg G, Schwartz GG, Szarek M, Hagström E. Patients with high genome-wide polygenic risk scores for coronary artery disease may receive greater clinical benefit from alirocumab treatment in the ODYSSEY OUTCOMES trial. *Circulation* 2020; **141**:624–636.
27. Aragam KG, Dobbyn A, Judy R, Chaffin M, Chaudhary K, Hindy G, Cagan A, Finneran P, Weng L-C, Loos RJF, Nadkarni G, Cho JH, Kember RL, Baras A, Reid J, Overton J, Philippakis A, Ellinor PT, Weiss ST, Rader DJ, Lubitz SA, Smoller JW, Karlson EW, Khera AV, Kathiresan S, Do R, Damrauer SM, Natarajan P. Limitations of contemporary guidelines for managing patients at high genetic risk of coronary artery disease. *Am Coll Cardiol* 2020;**75**:2769–2780.
28. Khan SS, Cooper R, Greenland P. Do polygenic risk scores improve patient selection for prevention of coronary artery disease? *JAMA* 2020;**323**:614–615.
29. Polygenic Risk Score Task Force of the International Common Disease Alliance. Responsible use of polygenic risk scores in the clinic: potential benefits, risks and gaps. *Nat Med* 2021;**27**:1876–1884.
30. Hadley TD, Agha AM, Ballantyne CM. How do we incorporate polygenic risk scores in cardiovascular disease risk assessment and management? *Curr Atheroscler Rep* 2021; **23**:28.
31. Kullo IJ, Jouni H, Austin EE, Brown S-A, Kruisselbrink TM, Isseh IN, Haddad RA, Marroush TS, Shameer K, Olson JE, Broeckel U, Green RC, Schaid DJ, Montori VM, Bailey KR. Incorporating a genetic risk score into coronary heart disease risk estimates: effect on low-density lipoprotein cholesterol levels (the MI-GENES clinical trial). *Circulation* 2016;**133**:1181–1188.
32. Knowles JW, Zarafshar S, Pavlovic A, Goldstein BA, Tsai S, Li J, McConnell MV, Absher D, Ashley EA, Kiernan M, Ioannidis JPA, Assimes TL. Impact of a genetic risk score for coronary artery disease on reducing cardiovascular risk: A pilot randomized controlled study. *Front Cardiovasc Med* 2017;**4**:53.
33. Mega JL, Stitziel NO, Smith JG, Chasman DI, Caulfield MJ, Devlin JJ, Nordio F, Hyde CL, Cannon CP, Sacks FM, Poulter NR, Sever PS, Ridker PM, Braunwald E, Melander O, Kathiresan S, Sabatine MS. Genetic risk, coronary heart disease events, and the clinical benefit of statin therapy: an analysis of primary and secondary prevention trials. *Lancet* 2015;**385**:2264–2271.
34. Marston NA, Kamanu FK, Nordio F, Gurmu Y, Roselli C, Sever PS, Pedersen TR, Keech AC, Wang H, Lira Pineda A, Giugliano RP, Lubitz SA, Ellinor PT, Sabatine MS, Ruff CT. Predicting benefit from evolocumab therapy in patients with atherosclerotic disease using a genetic risk score. Results from the FOURIER trial. *Circulation* 2020;**141**: 616–623.