Title:

Joint Association of Genetic Risk and Accelerometer-Measured Physical Activity with Incident Coronary Artery Disease in the UK Biobank Cohort

JAMA Card requirements:

3000 words

<= 5 tables and/or figures

**Currently at 2954 words and exactly 5 tables/figures**

**STRUCTURED ABSTRACT (up to 350 words):**

**Importance:**

Previous research demonstrates the joint association of self-reported physical activity, genetics with coronary artery disease. However, whether accelerometer-measured physical activity volume or intensity can offset genetic predisposition to coronary artery disease remains unexplored.

**Objective:**

To explore the independent and joint associations of accelerometer-measured physical activity and genetic risk with incident coronary artery disease.

**Design, Setting, and Participants:**

The UK Biobank population-based cohort recruited over 500,000 individuals ages 40 to 69 between 2006 and 2010, with 103,712 individuals participating in a wrist-worn accelerometer study from 2013 to 2015. 65,079 individuals of White British ancestry were included in the analytic sample, meeting the genotyping and accelerometer-based inclusion criteria and with no missing covariates.

**Main Outcomes and Measures:**

Incident coronary artery disease based on hospital inpatient records and death data serves as the outcome of this study. Polygenic risk score and physical activity volume and intensity are examined both continuously and by risk percentile with this continuous model.

**Results:**

In the sample of 65,079 individuals, the mean (SD) age was 62.51 (7.76) and 61% was female. During a median follow-up of 6.8 years, 1,382 cases of coronary artery disease developed. Physical activity intensity, measured as percent of physical activity of moderate-to-vigorous intensity, had a stronger association with coronary artery disease among individuals at the same genetic risk than physical activity volume, measured as physical activity energy expenditure, with a hazard ratio of 1.47 (95% CI: 1.28-1.68) at the 80th compared to 20th percentile of risk versus 1.31 (95% CI: 1.20-1.45). The combination of high genetic risk and low physical activity intensity produced the greatest risk, with an individual at the 80th percentile of risk for both categories facing a hazard ratio of 2.83 (95% CI: 2.40-3.32) compared to an individual at the 20th percentile of genetic and physical activity intensity risk.

**Conclusions and Relevance:**

Physical activity, especially physical activity intensity, ameliorates some of the genetic risk of coronary artery disease. This accelerometer-based study provides the clearest evidence to date regarding the joint influence of genetics and physical activity on coronary artery disease.

**KEY POINTS (75-100 words):**

**Question:** Canhigher levels of accelerometer-measured physical activity volume or intensity offset a high genetic predisposition to coronary artery disease?

**Findings:** In this population-based cohort of 65,079 individuals, physical activity volume and intensity were associated with lower levels of incident coronary artery diseasewithin genetic strata and the joint association of genetic risk and physical activity intensity had the largest association with incident coronary artery disease.

**Meaning:** High levels of accelerometer-measured physical activity may be beneficial, including for individuals at high genetic risk of coronary artery disease.

**INTRODUCTION**

Coronary artery disease (CAD) is a leading cause of death and disability worldwide.1,2 Both physical activity and genetic risk play a crucial role in its development.3,4 Decades of evidence demonstrate the importance of physical activity volume and intensity in reducing the risk of CAD.4–7 However, in recent years, large-scale studies with accelerometer-measured physical activity suggest both that the benefits of physical activity in reducing the risk of CAD may be greater than previously realized and physical activity intensity and volume may each contribute to this risk reduction.8–11

While genetic susceptibility to CAD was established decades ago by twin studies, recent genome-wide association studies have identified millions of variants associated with CAD.3,12,13 Methods of combining these variants have enabled the construction of increasingly predictive polygenic risk scores that improve researchers’ ability to discern the genetic risk of developing CAD.14,15

Several studies have explored the impact of genetic susceptibility and self-reported lifestyle factors, including physical activity, on cardiovascular diseases.9,16–20 Genetic risk and physical activity had independent associations with cardiovascular disease and jointly further increased overall risk in each study. However, these studies relied on questionnaire-assessed physical activity defined either dichotomously or as quantiles. Modeling physical activity dichotomously or in quantiles ignores the continuous relationship between physical activity and CAD risk.4,10 Because these quantiles group physical activity intensity and volume together, these previous efforts could not distinguish their relative importance.9

This subjective measure of physical activity has several limitations. In doubly labeled water studies, the gold standard to assess physical activity energy expenditure (PAEE), questionnaire-assessed physical activity demonstrated a weaker correlation with PAEE than objective measures.21,22 This method also does not account for incidental physical activity throughout the day and administering longer questionnaires to provide a more holistic view of an individual’s daily physical activity results in higher levels of misclassification.23,24 Even when administered by a trained professional, questionnaire-based techniques suffer from recall and social desirability bias and perform differentially well in people of different sociodemographic backgrounds.25,26 These sources of bias may obscure the relationship between physical activity, genetic risk, and incident CAD.

This study evaluated the extent to which objective physical activity volume and intensity, measured by a wrist-worn accelerometer and modeled continuously, can offset an individual’s genetic susceptibility to incident CAD in the UK Biobank.27 We utilized the best performing polygenic risk score to date, allowing for more precise genetic risk stratification than in previous efforts. Secondarily, we explored whether a gene-environment interaction exists between physical activity volume and intensity and genetic risk.

**METHODS**

*Accelerometer Cohort*

We used the UK Biobank (application # 79654), a population-based cohort of over 500,000 individuals from England, Scotland, and Wales aged 40-69 at recruitment between 2006 and 2010. Follow-up time was censored on March 31st, 2016 in Wales, September 30th, 2021 in England, and July 31, 2021 in Scotland. This dataset contains information on genetics, health behaviors, socioeconomic status, and health status and is described in detail elsewhere.27 Between 2013 and 2015, Participants with an email address outside the North West region were invited and a subsample of 103,712 individuals responded to an email recruiting them to wear a wrist-worn Axivity AX3 triaxial accelerometer continuously for seven days on their dominant wrist and provided data. We applied exclusion criteria used previously in this dataset and dropped participants who failed calibration, had implausibly high overall acceleration averages, had wear time under three days, or did not have 24 unique hours of wear in a 24-hour cycle.28,29

*Genotyping & Imputation*

Participants in the UK Biobank were genotyped using either the UK BiLEVE or the UK Biobank Axiom Array, which each genotyped over 800,000 single-nucleotide polymorphisms (SNPs). Using either the Haplotype Reference Consortium panel or the UK10k and 1000 Genomes phase 3 panels, additional SNPs were imputed, yielding roughly 96 million variants assayed or imputed.30 Following standard genetic quality control criteria in this dataset, we dropped individuals who withdrew consent or were not genotyped, had a mismatch between genetic and reported biological sex, sexual aneuploidy, outliers for missingness or heterozygosity, and we limited the dataset to the maximal set of individuals not related by third degree or closer.31 We also split the dataset by ancestry, with those of White British ancestry as the sample for the primary analyses. Black or Asian ancestry individuals contribute too few cases for formal analyses.

*Polygenic Score*

We applied the most predictive polygenic risk score available for CAD.14 This score was derived by obtaining weights from the largest European-ancestry focused GWAS excluding the UK Biobank; and used PRS-CS, a polygenic risk score prediction method utilizing a Bayesian framework and continuous shrinkage robust to varying genetic architecture. We screened out multi-allelic SNPs, restricted to SNPs with an INFO score greater than 0.6, and restricted minor allele frequency to at least 0.01, yielding 1,087,647 variants included in the score. We then applied the scoring file available on PGS Catalog to recreate the scores derived in the original study.32 We transformed the score into zero mean and unit variance.

*Physical Activity Measures*

Previous researchers processed the raw accelerometer data in the UK Biobank by calibrating to local gravity, filtering out sensor noise and gravity, and detecting and imputing non-wear time data segments to calculate the Euclidean norm minus one (ENMO).28,33 The average ENMO was summarized as an average proportion of daily time spent at different categories of intensity measured in milligravities (mgs) based on measurements taken every 5 seconds. Following Dempsey *et al*., we used a formula shown in **eTable 1** to convert these categorical midpoints of ENMO from dominant wrist-worn accelerometer data into instantaneous physical activity energy expenditure (PAEE).11 This measure was validated in free-living populations by both doubly labeled water and a combined heart rate monitor and trunk acceleration, the gold and silver standards of physical activity energy expenditure measurement, respectively.21,34,35 PAEE serves as our measure of physical activity volume in kJ/kg/day. In order to calculate physical activity intensity, we categorized physical activity above 125 milligravities as moderate-to-vigorous physical activity (MVPA) and then divided this value by total PAEE and multiplied by 100 to yield the percentage of PAEE from MVPA (percent MVPA).10,11,21,36

*Outcome Definition*

We defined CAD based on hospital inpatient episodes, surgeries, and deaths. Specifically, we used ICD-10 codes I20 to I25, I46, and R96 to determine CAD as a cause of death, ICD-10 codes I20.0, I21-I22, and ICD-9 codes 410 and 4110 to denote a CAD event in hospital inpatient records, and OPCS-4 codes K40 to K46, K49, K501, K75 and OPCS-3 code 3043 to denote a CAD-related surgery. We restricted to incident CAD by excluding individuals with an event prior to the start of accelerometer wear. **eFigure 1** shows the Kaplan-Meier plot for survival in the sample.

*Covariates*

In several waves, participants self-reported information on diet, health behaviors, parental heart disease history, mobility, employment status, and educational attainment pertinent to this analysis. These questionnaires did not occur at the same time as accelerometer wear. To minimize the bias from this discrepancy, we chose the value of the covariates from the most recent wave of self-reported data before accelerometer wear began. Diet consists of several variables, including whether an individual often adds salt to their food, past day consumption of fruits and vegetables, and weekly consumption frequency of oily fish and processed meat. Educational attainment is measured as whether a person has a university degree, any other degree, or no degree. Health behaviors include smoking status divided into never, previous, or current and alcohol consumption measured as frequency of consumption per week. Employment status determines whether an individual is currently employed, and mobility problems denotes whether an individual has indicated any issues walking. **eTable 2** shows how we created these variables from UK Biobank data fields. We controlled for the first 10 genetic principal components, region, biological sex, the Townsend index, and season of wear, which as static variables did not depend on the wave selected.

*Statistical Analyses*

We applied a Cox proportional hazards model with age as the timescale to measure the association between physical activity volume and intensity, genetic risk, and incident CAD with time-to-event as the outcome of interest. The model stratified on covariates violating the proportional hazards assumption based on Schoenfeld residuals. Because the functional form of physical activity volume and intensity’s relationship with CAD could be nonlinear, we tested model fit between the exposures entering the model linearly or as a restricted quadratic or cubic spline. The linear model performed best for both physical activity exposures according to BIC. We ran the model with PAEE and polygenic risk score as continuous exposures controlling for age and sex and then with the full covariate set. Using this continuous model, hazard ratios and 95% confidence intervals were then calculated based on genetic and physical activity volume risk percentiles for the 20th and 80th percentile of risk with the 20th percentile of risk (lowest) in both serving as the reference group. We restricted to the 20th and 80th percentiles of risk instead of the maximum and minimum to avoid interpreting results based on the sparsely populated extremes of the distributions. We ran a model with percent MVPA and polygenic risk score as continuous exposures controlling for PAEE and again adjusting for age and sex and then the full covariate set and repeated the percentile-based analysis. In sensitivity analyses, we excluded cases occurring within the first year of accelerometer wear to minimize possible reverse causation, explored the impact of measured body mass index, average sleep duration, and cholesterol and blood pressure medication, all potential mediators, as well as manual labor conducted for one’s occupation on the results. We relied on complete case analysis but imputed via multivariate imputation by chained equations as a sensitivity analysis.

We explored whether genetic risk and physical activity volume and intensity interact to increase risk of incident CAD by fitting interaction terms between the PA exposures and the polygenic risk score. All analyses were performed using R 4.1.3.37 All code is available on GitHub at XXX.

**RESULTS**

*Population Characteristics*

After screening individuals for valid accelerometer wear data, 96,660 participants remained in the study. We excluded 17,206 participants not meeting the genetic quality control criteria. 1,587 participants had missing covariate data, and 1,980 had prevalent CAD at baseline, which left a final analytic sample of 75,887, among whom 65,079 participants were of White British ancestry as outlined in **Figure 1**. Compliance was high, with a median wear time of 6.9 days. **Table 1** shows the characteristics of the participants in our sample. The median follow-up time was 6.8 years with a total of 430,160 cumulative person-years and 1,368 CAD cases. The average age at baseline was 62.5 and participants in this sample were generally higher educated, less likely to smoke, and had lower levels of material deprivation than the larger population in the UK, which coheres with previous research.38 **eTable 3** shows the percentiles of PAEE, % MVPA, and the polygenic score. Model 1 refers to the fully adjusted model and model 0 refers to the model adjusted for biological sex.

**[Insert Figure 1 here]**

**[Insert Table 1 here]**

*Raw Associations of Genetic Risk, Physical Activity, and Incident CAD*

As **eTable 4** demonstrates, the hazard ratio for a standard deviation increase in polygenic risk is 1.49 (95% CI: 1.41-1.58) in model 1. The hazard ratio from a standard deviation increase in PAEE is 0.84 (95% CI: 0.79-0.89) and for percent MVPA 0.80 (95% CI: 0.74-0.86), which includes PAEE as a confounder, in model 1. **eTable 5** presents results for model 0.

*Physical Activity Volume & Genetic Risk Percentile Comparison*

**Table 2** and **Figure 2** present the hazard ratios of participants at different genetic and PAEE risk percentiles, with a lower percentile denoting a lower risk of incident CAD. All results are for model 1. Hazard increases substantially at the highest levels of inactivity, with an individual at the 80th percentile of PAEE risk facing a 31% greater hazard of incident CAD compared to an individual of the same genetic risk at the 20th percentile of PAEE. Genetic risk has a stronger association as an individual at the 80th percentile of genetic risk within the same PAEE stratum faces a 92% greater hazard of incident CAD than if they were in the 20th percentile of genetic risk. While PAEE and genetic risk each have important independent associations with incident CAD, they combine to create the highest risk of incident CAD. An individual at the 80th percentile of risk for PAEE and genetic susceptibility faces a 153% greater hazard of incident CAD than the reference group.

**[Insert Table 2 here]**

*Physical Activity Intensity & Genetic Risk Percentile Comparison*

Controlling for PAEE in model 1, **Table 3** shows that percent MVPA has a stronger association with incident CAD than PAEE. An individual at the 80th percentile of percent MVPA risk faces a 47% greater hazard of incident CAD compared to an individual of the same genetic risk at the 20th percentile. The combined association between a participant at the 80th percentile of risk for both percent MVPA and genetic susceptibility results in nearly three times higher hazard of incident CAD relative to an individual in the reference group. We explored possible interaction between physical activity volume and intensity and concluded that no significant interaction exists in this sample.

**[Insert Table 3 here]**

**[Insert Figure 2 here]**

*PA Volume/Intensity Interaction with Genetic Risk*

In **eTable 6** we found no significant interactions between PAEE and genetic risk or percent MVPA and genetic risk. This coheres with the existing literature relying on subjective physical activity and genetic risk.9,19

*Sensitivity Analyses*

We excluded individuals with cases occurring within the first year of follow-up in **eTables 7 and 8**, reran the analyses with multivariate imputation by chained equations in **eTables 9 and 10**, and added potential mediators and occupation into the model with results in **eTables 11 and 12**. None of these choices substantially affected the results.

**DISCUSSION**

*Overview of Principal Findings*

In this study of 66,180 participants from the UK Biobank, genetic risk was associated with a higher risk of incident CAD regardless of physical activity volume or intensity. Physical activity volume and intensity each had important independent associations with incident CAD, with physical activity intensity demonstrating the strongest association. While low physical activity volume and intensity increased risk of CAD within a genetic risk stratum, low levels of physical activity volume and intensity were associated with greater risk of incident CAD in the highest genetic risk group. This suggests that physical activity behavior can play a role in abating high genetic risk of CAD. Specifically, an individual at the 80th percentile of genetic risk and 20th percentile of physical activity volume or intensity risk in the percentile analysis faced a 92% greater hazard of CAD compared to a 153% increase and 183% increase if they also had 80th percentile levels of physical activity volume or intensity, respectively.

*Comparison with Existing Literature*

Compared to previous studies on subjective physical activity, genetic risk, and cardiovascular diseases, the association between CAD and genetic risk is stronger in the current study.9,19 Because previous studies discretize subjective physical activity, a direct comparison to estimates from the existing literature is not possible. However, the estimates for physical activity’s association with cardiovascular diseases in Said, *et al*. and Tikkanen *et al.* appear consistent with this study.9,19 Zaccardi *et al*., rely on self-reported walking pace as the measure of physical activity and show that this has a large association with CAD, which is also consistent with our stronger results for physical activity intensity.20 Because none of these studies separate physical activity volume and intensity, we demonstrate that intensity may supersede volume in terms of reducing risk of CAD from a high genetic risk. Our results within genetic risk strata largely agree with existing accelerometer-based studies, although we model physical activity volume and intensity linearly.10,11

*Strengths & Limitations*

This is the first study to explore the association of genetic risk and accelerometer-measured physical activity volume and intensity with incident CAD. We use the strongest polygenic risk score and the largest sample of individuals with accelerometer measurements to date. By modeling physical activity continuously and objectively, we avoid the significant misclassification problems from discretizing subjective physical activity.39,40 The exploding commercial popularity of wrist-worn accelerometers has decreased the relevance of current physical activity standards for the population relying on these devices.41–43 By measuring incidental physical activity, accelerometers overestimate the number of people reaching conventional physical activity standards and studies relying on accelerometer-measured physical activity can help close this gap.41

This study has several limitations. The UK Biobank sample is disproportionately White and affluent relative to the general population and the sample who responded to take place in the accelerometer study represents further selection bias. However, previous studies have found in terms of physical activity, this cohort appears representative of the general population.44 The covariates used rely on self-reporting and are measured at different times than accelerometer wear. Accelerometer wear occurred over seven days, which makes it a cross-sectional measure, although we validate this against two waves of subjective physical activity in **eFigure 3**. Previous studies have shown that reactivity, or a behavioral response to accelerometer wear, may bias measured physical activity volume, although not MVPA.45 Because physical activity is not determined randomly, unmeasured confounding exists. More sophisticated machine learning methods can better discriminate between activity types and studies have shown our method of segregating percent MVPA is prone to misclassification.46,47 Wrist-worn accelerometers have limited ability to capture all physical activity, with housework, cycling, and weightlifting especially poorly captured.48,49

*Conclusion*

High genetic risk and low levels of physical activity volume and intensity were associated with large increases in incident CAD. This study showed physical activity is beneficial regardless of an individual’s underlying genetic risk and that genetic risk does not determine an individual’s fate regarding CAD, which makes disclosure of genetic risk to patients only after a nuanced discussion of their interpretation essential.50

**REMOVED:**

*Interpretation*

In order to ground this quintile analysis in more readily recognized terms, we convert PAEE into kcal/day for a 75-kilogram individual. The 80th percentile of PAEE risk corresponds to 539 kcal/day from physical activity for a 75 kg individual compared to 869 kcal/day at the 20th percentile of PAEE risk. Likewise, for an individual at the 20th percentile of PAEE risk, 80th percentile percent MVPA risk corresponds to 140 kcal/day from MVPA compared to 245 kcal/day from MVPA in the 20th percentile.

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**FIGURES & TABLES**

**Figure 1: Subject Exclusion Criteria Flowchart**

Diagram

Description automatically generated

**Table 1: Summary Statistics**

|  |  |  |
| --- | --- | --- |
| **Summary Statistics (n = 65,079; Incident CAD = 1368)** | | |
| *Variable* |  |  |
| Follow-up Time, median(IQR) |  | 6.82 (6.29, 7.36) |
| Physical Activity Energy Expenditure (PAEE), mean(SD) |  | 39.56 (11.49) |
| Percent moderate-to-vigorous physical activity (percent MVPA), mean(SD) |  | 35.79% (11.39) |
| Standardized Polygenic Risk Score, mean(SD) |  | 0 (1.00) |
| Person-Years |  | 430,160 |
| Age, mean(SD) |  | 62.51 (7.76) |
| **Highest Education Level, n(%)** |  |  |
|  | *University* | 27,779 (42.69%) |
|  | *Any Other Qualification* | 32,076 (49.29%) |
|  | *No qualification* | 5,224 (8.03%) |
| Townsend Index, mean(SD) |  | -1.92 (0.08) |
| Currently Employed, n(%) |  | 38,614 (59.33%) |
| Fruit & Vegetable Intake Quartile, mean(SD) |  | 2.10 (0.59) |
| Weekly Alcohol Consumption, mean(SD) |  | 3.02 (0.58) |
| Weekly Oily Fish Consumption, mean(SD) |  | 1.10 (1.00) |
| Female, n(%) |  | 36,790 (61.14%) |
| Parental History of Heart Disease, n(%) |  | 26,737 (41.08%) |
| **Cigarette Smoking Status, n(%)** |  |  |
|  | *Never* | 37,773 (58.04%) |
|  | *Previous* | 23,166 (35.60%) |
|  | *Current* | 4,140 (6.36%) |
| **Added Salt Intake, n(%)** |  |  |
|  | *Never* | 39,573 (60.81%) |
|  | *Rarely* | 17,085 (26.25%) |
|  | *Sometimes* | 6,561 (10.08%) |
|  | *Always* | 1,860 (2.86%) |
| **Season Accelerometer Worn, n(%)** |  |  |
|  | *Fall* | 19,329 (29.70%) |
|  | *Spring* | 14,810 (22.76%) |
|  | *Summer* | 17,086 (26.25%) |
|  | *Winter* | 13,854 (21.29%) |
| **Region, n(%)** |  |  |
|  | *England* | 58,225 (89.47%) |
|  | *Scotland* | 4,322 (6.64%) |
|  | *Wales* | 2,532 (3.89%) |
| Mobility Limitations, n(%) |  | 12,676 (19.48%) |

**Table 2: Overview of Physical Activity Volume and Genetic Susceptibility Results**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Genetic Risk Quintile** | **Physical Activity Energy Expenditure Risk Quintile** | | | |
| *20th Percentile* | *40th Percentile* | *60th Percentile* | *80th Percentile* |
| *20th Percentile* | 1 (Reference) | 1.11 (95% CI: 1.07-1.15) | 1.21 (95% CI: 1.13-1.29) | 1.31 (95% CI: 1.20-1.45) |
| *40th Percentile* | 1.26 (95% CI: 1.22-1.30) | 1.40 (95% CI: 1.33-1.46) | 1.51 (95% CI: 1.41-1.63) | 1.65 (95% CI: 1.49-1.82) |
| *60th Percentile* | 1.53 (95% CI: 1.44-1.63) | 1.71 (95% CI: 1.59-1.83) | 1.85 (95% CI: 1.70-2.02) | 2.02 (95% CI: 1.81-2.26) |
| *80th Percentile* | 1.92 (95% CI: 1.77-2.10) | 2.14 (95% CI: 1.94-2.36) | 2.32 (95% CI: 2.08-2.59) | 2.53 (95% CI: 2.22-2.88) |

**Table 3: Overview of Physical Activity Intensity and Genetic Susceptibility Results**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Genetic Risk Quintile** | **Percent Moderate-to-Vigorous Physical Activity Risk Quintile** | | | |
| *20th Percentile* | *40th Percentile* | *60th Percentile* | *80th Percentile* |
| *20th Percentile* | 1 (Reference) | 1.15 (95% CI: 1.09-1.20) | 1.29 (95% CI: 1.18-1.41) | 1.47 (95% CI: 1.28-1.68) |
| *40th Percentile* | 1.26 (95% CI: 1.22-1.30) | 1.44 (95% CI: 1.36-1.52) | 1.62 (95% CI: 1.47-1.77) | 1.84 (95% CI: 1.61-2.12) |
| *60th Percentile* | 1.54 (95% CI: 1.45-1.63) | 1.77 (95% CI: 1.64-1.91) | 1.99 (95% CI: 1.79-2.21) | 2.27 (95% CI: 1.96-2.63) |
| *80th Percentile* | 1.92 (95% CI: 1.76-2.11) | 2.20 (95% CI: 1.99-2.44) | 2.48 (95% CI: 2.18-2.81) | 2.83 (95% CI: 2.40-3.32) |

**Figure 2: Forest Plots of Genetic Risk and Physical Activity and Incident CAD**

**A**

|  |
| --- |
| ***20th Percentile of Genetic Risk vs 40th Genetic Risk***  A picture containing scatter chart  Description automatically generated |
| ***20th Percentile of Genetic Risk vs 60th Percentile of Genetic Risk***  A picture containing chart  Description automatically generated |
| ***20th Percentile of Genetic Risk vs 80th Percentile of Genetic Risk***  A picture containing timeline  Description automatically generated |
|  |

**B**

|  |
| --- |
| ***20th Percentile of Genetic Risk vs 40th Genetic Risk***  A picture containing box and whisker chart  Description automatically generated |
| ***20th Percentile of Genetic Risk vs 60th Percentile of Genetic Risk***  Chart, box and whisker chart  Description automatically generated |
| ***20th Percentile of Genetic Risk vs 80th Percentile of Genetic Risk***  Chart  Description automatically generated |
|  |