Title:

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

JAMA Card requirements:

3000 words

<= 5 tables and/or figures

**Currently at 3404 words and exactly 5 tables/figures**

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

**Importance:**

Genetics and physical activity are established risk factors for 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 between accelerometer-measured physical activity volume and intensity and genetic risk and 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. A total of 65,079 individuals of White British ancestry were included in the study who met the genotyping and accelerometer-based inclusion criteria and had no missing covariates.

**Main Outcomes and Measures:**

Incident coronary artery disease based on hospital inpatient records, death data, and self-report serves as the outcome of this study. The association between incident coronary artery disease and genetic risk and physical activity volume and intensity is examined both continuously and by risk quintile with this continuous model.

**Results:**

In the final sample of 65,079 individuals, the mean (SD) age was 62.51 (7.76) and 61% of the sample was female. During a median follow-up of 6.8 years, 1,382 cases of coronary artery disease developed. Within a genetic risk stratum, Physical activity intensity, measured as percent of physical activity of moderate-to-vigorous intensity, had a stronger association with coronary artery disease 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 physical activity intensity versus 1.31 (95% CI: 1.20-1.45). The combination of high genetic risk and low physical activity intensity produced the greatest overall 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 risk.

**Conclusions and Relevance:**

Physical activity, especially physical activity intensity, appears beneficial regardless of an individual’s coronary artery disease genetic risk. Patients at high genetic risk may particularly benefit from moderate-to-vigorous physical activity and wrist-worn accelerometers can help track their progress.

**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, especially for individuals at high genetic risk of coronary artery disease.

**INTRODUCTION**

Coronary artery disease (CAD) is one of the leading causes of death and disability worldwide.1,2 Both physical activity and underlying genetic risk play a crucial role in its development.3,4 Decades of evidence have demonstrated the importance of physical activity volume and intensity in reducing the risk of CAD and cardiovascular diseases more broadly.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 even greater than previously realized and that physical activity intensity and volume may each contribute to this risk reduction.8–11

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

Several studies have explored the impact of genetic susceptibility and self-reported lifestyle factors, which included physical activity, on cardiovascular diseases.9,16–20 Each study found that genetic risk and physical activity had independent associations with cardiovascular disease and jointly produced an even greater overall risk. However, these studies relied on questionnaire-assessed physical activity defined either dichotomously or split into 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 also could not distinguish their relative importance.9

More significantly, 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 far weaker correlation with PAEE than objective measures do.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 with the help of a trained professional, questionnaire-based techniques still suffer from recall and social desirability bias and perform differentially well in people of different sociodemographic backgrounds.25,26 These many potential sources of bias may obscure the relationship between physical activity, genetic risk, and incident CAD.

This study primarily aimed to evaluate 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, which allowed for more precise genetic risk stratification than in previous efforts. Secondarily, we explore whether a gene-environment interaction exists between physical activity volume and intensity and genetic risk.

**METHODS**

*Study Sample*

*Accelerometer Cohort*

We used the UK Biobank (application # 79654), a population-based cohort of over 500,000 individuals from England, Scotland, and Wales who were 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 for hospital inpatient records. This dataset contains in-depth information on genetics, health behaviors, socioeconomic status, and health status and has been described in detail elsewhere.27 Between 2013 and 2015, 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 (over 100 milligravities), 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 Axiom Array 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, which yielded roughly 96 million total variants either directly identified or imputed.30 Following the standard genetic quality control criteria in this dataset, we dropped individuals who withdrew consent or were not genotyped, those with a mismatch between genetic and reported biological sex, sexual aneuploidy, outliers for missingness or heterozygosity, and 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 serving as the sample for the primary analyses and Black or Asian ancestry individuals for exploratory analyses in **eFigure 2**.

*Polygenic Score*

We applied the most recent and predictive polygenic risk score available for CAD, which was tested but not trained on UK Biobank data.14 Briefly, this score was derived by obtaining weights from the largest European-ancestry focused GWAS that excluded the UK Biobank and used PRS-CS, a polygenic risk score prediction method that utilizes a Bayesian framework and continuous shrinkage that is robust to varying genetic architecture and has shown advantages in the prediction of CAD over more traditional methods. We screen out multi-allelic SNPs, restrict to only SNPs with an INFO score, a measure of imputation quality, of greater than 0.6, and restrict minor allele frequency to at least 0.01, which yields 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 Finally, we transformed the score into zero mean and unit variance for ease of interpretation.

*Physical Activity Measures*

Previous researchers have 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 the work of Dempsey *et al*., we used a formula to convert these categorical midpoints of ENMO from dominant wrist-worn accelerometer data into instantaneous physical activity energy expenditure (PAEE).11 This measure has been 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 Overall PAEE serves as our measure of total physical activity volume in kJ/kg/day with the formula used in **eTable 1**. In order to calculate physical activity intensity, we categorized all physical activity above 125 milligravities as moderate to vigorous physical activity (MVPA) and then divided this value by the total physical activity volume 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, deaths, and, if none of the rest are available, by self-report. 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 then restricted cases to only incident CAD by excluding individuals who experienced an event prior to the start of accelerometer wear. Kaplan-Meier estimates for survival in the sample are available in **eFigure 1**.

*Covariates*

In several waves, participants self-reported information on diet, health behaviors, parental history of heart disease, 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 that occurred 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, another kind of 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. An explanation of how we created these variables from the UK Biobank is in **eTable 2**. We also 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 that violated 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 as opposed to as a restricted quadratic or restricted cubic spline. The linear model performed best for both physical activity exposures according to BIC criteria. Next, a model was run with PAEE and the polygenic risk score as continuous exposures with only age and sex and then with the full set of covariates. Genetic risk and physical activity volume risk were then split into quintiles and hazard ratio and 95% confidence intervals were calculated with the 20th percentile of risk (lowest) in both serving as the reference group. We then 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 set of covariates. We then repeated the quintile-based analysis using percent MVPA and adjusted for PAEE. We conducted sensitivity analyses excluding cases that occurred within the first year of accelerometer wear to minimize the potential for reverse causation. In additional sensitivity analyses, we 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.

Lastly, we explored the possibility that genetic risk and physical activity volume and intensity interact to produce a higher 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. A further 17,206 participants were excluded who did not meet the genetic quality control criteria. 1,587 participants were excluded who had missing covariate data, and 1,980 who 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 since accelerometer wear began was 6.8 years with a total of 430,160 cumulative person-years and 1,368 incident CAD cases occurred. The average age at baseline was 62.5 years old 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 demonstrating the relative health and high socioeconomic status of UK Biobank participants.38 The quintiles of PAEE, % MVPA, and the polygenic score are available in **eTable 3**. Model 1 refers to the fully adjusted model and model 0 refers to the model adjusted only 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. As expected, this effect is even stronger than in previous studies on CAD, genetic risk, and lifestyle.16,19 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 the fully adjusted model. The results for model 0 (adjusted for biological sex only) are present in **eTable 5**.

*Physical Activity Volume & Genetic Risk Quintile Comparison*

**Table 2** and **Figure 2** present the hazard ratios of participants at different genetic and PAEE risk quintiles, with a lower quintile denoting a lower risk of incident CAD. All results are for model 1 (full adjustment). PAEE and genetic risk at every quintile beyond the 20th percentile exhibited significant differences with the reference group, which emphasizes that even small changes in genetic risk or PAEE could have meaningful effects on an individual’s overall risk. 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 in the same genetic risk stratum at the 20th percentile of PAEE. Genetic risk has an even 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. The absolute hazard from a lack of physical activity becomes far greater at higher genetic risk groups. Specifically, an individual at the 80th percentile of risk for PAEE and genetic susceptibility faces a 153% greater hazard of incident CAD than an individual in the 20th percentile of risk in both categories compared to the reference group.

**[Insert Table 2 here]**

*Physical Activity Intensity & Genetic Risk Quintile Comparison*

Controlling for physical activity volume in model 1, **Table 3** shows that percent MVPA has an even 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 in the same genetic risk stratum at the 20th percentile of percent MVPA risk, which surpasses the risk from comparatively low levels of PAEE. The combined association between a participant in the 80th percentile of risk for both percent MVPA and genetic susceptibility results in nearly three times higher hazard of incident CAD than for an individual in the reference group. We explored possible interaction between physical activity volume and intensity and concluded that no significant interaction appears to exist in this sample.

**[Insert Table 3 here]**

**[Insert Figure 2 here]**

*PA Volume/Intensity Interaction with Genetic Risk*

We found no significant interactions between either PAEE and genetic risk or percent MVPA and genetic risk as seen in **eTable 6**. This coheres with the existing literature that relied on subjective physical activity and genetic risk in larger samples.9,19 Although the smaller sample would increase the difficulty of detecting an effect, the preponderance of this evidence suggests that any interaction effect that might exist between physical activity and genetic risk is likely small.

*Sensitivity Analyses*

We perform a host of sensitivity analyses to test the stability of these results. We excluded individuals with cases that occurred within the first year of follow-up, reran the analyses with imputation, and added potential mediators and occupation into the model with results available in **eTables 7 to 12**. None of these choices had a substantial effect on the results.

**DISCUSSION**

*Overview of Principal Findings*

In this study of 66,180 participants from the UK Biobank, the largest accelerometer-measured cohort in existence, 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 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 an even greater risk of incident CAD in the highest genetic risk group. This suggests that physical activity behavior plays a large role in abating high genetic risk of CAD. Specifically, an individual at the highest level of genetic risk and lowest level of physical activity volume or intensity in the quintile analysis faced a 92% greater hazard of CAD compared to a 153% increase and a 183% increase if they also had the lowest levels of physical activity volume or intensity, respectively. No interactions either between physical activity volume and intensity or between physical activity and genetic risk were observed.

*Comparison with Existing Literature*

This is the first study to explore the association of genetic risk and accelerometer-measured physical activity with incident CAD. While a comparison to previous studies on subjective physical activity, genetic risk, and cardiovascular diseases is challenging, the association between CAD and genetic risk appears stronger in the current study.9,19 In Said et al., physical activity was discretized into ideal, intermediate, and poor with ideal denoting that a person met AHA standards and poor denoting a person engaged in no MVPA. While the association between ideal and poor is even stronger than observed in our study, this likely occurs because the comparison includes individuals at the absolute extreme of physical activity, whereas we observe as a worst-case scenario individuals at the 80th percentile. In contrast, in Tikkanen, which split subjective physical activity into tertiles, the differences between high and low levels of physical activity within genetic risk groups are far smaller than those observed in the present study. Relative to existing accelerometer-based studies, our results within genetic risk strata largely agree with these studies, although we model physical activity volume and intensity linearly.10,11

*Strengths & Limitations*

This study was the first to compare accelerometer-measured physical activity volume and intensity and genetic risk’s association with incident CAD. We made use of the strongest polygenic risk score to date in the largest sample of individuals with accelerometer measurements in existence. By modeling physical activity continuously and with accelerometer measurements, we avoid the significant misclassification problems that can occur when discretizing subjective physical activity.39,40 Lastly, the exploding popularity of commercially used wrist-worn accelerometers has made current physical activity standards less relevant for the population who rely on these devices.41–43 By measuring incidental physical activity, accelerometers would far overestimate the number of people reaching physical activity standards by conventional standards and studies relying explicitly on accelerometer-measured physical activity can help close this gap.41

There are numerous limitations of the present study. The UK Biobank sample is already disproportionately White and affluent relative to the general population and the sample who responded to take place in the accelerometer study represents further possibility for selection bias. However, previous studies have found that at least in terms of physical activity, this cohort appears representative of the general population.44 The covariates in the study rely on self-reporting and are not measured at the same time as accelerometer wear, which could lead to persisting residual confounding. Accelerometer wear also occurred only over a period of seven days, which makes it a cross-sectional measure, although we validate this against longitudinal measures of subjective physical activity in **eFigure 3**. Previous studies have shown that reactivity bias, or a behavioral response to accelerometer wear, may bias measured physical activity volume, although not MVPA.45 This is an observational study and because physical activity volume and intensity are not determined randomly, it is likely confounding still exists. More sophisticated machine learning methods are being developed to better discriminate between different activity types and studies have shown this method of segregating % MVPA is prone to misclassification.46,47 Lastly, wrist-worn accelerometers are limited in their ability to capture all forms of 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 a large increase in incident CAD. This study showed that 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) |
| PAEE, mean(SD) |  | 39.56 (11.49) |
| 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 of Wear, 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 |
|  |