Title? Joint association of genetic susceptibility and objectively measured physical activity with incident CAD?

Genetic Risk, Objectively Measured PA, and Incident CAD?

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

Accelerometer-measured?

PA Intensity and Volume?

Genetic Risk, Objectively Measured Physical Activity, and Incident Coronary Artery Disease?

Literature Reviewed and To Review for Paper 3

*SNOWBALL SAMPLE AS THIS GOES*

***Justification of PA Measurement - Why Physical Activity Energy Expenditure (PAEE) and why %MVPA and % Vigorous?***

***ALL OF THESE STUDIES \*IN FREE-LIVING POPULATIONS\* - THIS is the real innovation of PA measurement in past several years***

***PAEE Units = J/min/KG (converted to KJ/day/KG)***

***General Explanation:***

***PAEE was validated against heart rate and thigh accelerometer in UK population w/ gold-standard doubly labeled water study, so gets closer to what we mean when we say MVPA (heart rate changes often…). MVPA and Vigorous because COMPOSITION of PA seems to matter at least as much as overall PA for heart health***

“Estimation of Physical Activity Energy Expenditure during Free-Living from Wrist Accelerometry in UK Adults”

PLOS ONE, 2016

White et al

Goal: Explores the relationship between wrist acceleration and PAEE

Study Design: 1,695 individuals wore a nondominant-wrist accelerometer and a sensor that measured heart rate and trunk acceleration over the course of six days. Combined sensor with treadmill test to produce individually-calibrated PAEE. Trained on 60% of data and tested on remaining 40%.

Results: Wrist acceleration explained 44-47% of between-individual variance in PAEE. This doesn’t sound super high but FAR better than subjectively measured PA…

Conclusions: STRONG relationship between wrist-worn accelerometry and PAEE - in FREE-LIVING adult population in the UK

Why equation instead of just using ENMO? Because relationship between PAEE and wrist-worn accelerometer data is CURVILINEAR not LINEAR…

ALSO \*NO\* significant biases by age, slight differences by gender

“Estimating energy expenditure from wrist and thigh accelerometry in free-living adults: a doubly labelled water study”

Int J Obesity, 2019

White et al.

Goal: Assessing the validity of wrist-worn accelerometry data for PAEE using gold-standard of doubly labeled water. ALSO IS THE SOURCE THAT PROVIDES THE WRIST-WORN ACCELEROMETER TO PAEE EQUATION.

Study Design: 193 adults living in the UK w/ triaxial accelerometers on BOTH dominant AND nondominant wrists, as well as right thigh, in **free-living** conditions for 9-14 days.

Results: “Mean TEE and AEE derived from DLW (doubly-labeled water) were 11.6 (2.3) MJ day−1 and **49.8** (16.3) kJ day−1 kg−1… Estimates of AEE were **48.6** (11.8) kJ day−1 kg−1 from dominant wrist, 48.6 (12.3) from non-dominant wrist, and 46.0 (10.1) from thigh; these agreed strongly with AEE (RMSE ~12.2 kJ day−1 kg−1, r ~ 0.71) with small mean biases at the population level (~6%).

Note: Here TEE = total energy expenditure and AEE = active energy expenditure

**Conclusions: Wrist-worn accelerometer data can be used to estimate PAEE with V HIGH LEVEL OF PRECISION as confirmed by GOLD-STANDARD DLW STUDY**

“…applied to ENMO at 5-s resolution yielded a valid activity energy expenditure estimate, with a small mean bias and a RMSE of 13 kJ day−1 kg−1 and moderately high correlation (*r* = 0.61).” This is explicitly about UK Biobank usage… But they also note that moderate in this instance corresponds to approximately 159 mgs

FASCINATING AID TO IMPORTANCE OF PA INTENSITY ARGUMENT:

“Walking pace improves all-cause and cardiovascular mortality risk prediction: A UK Biobank prognostic study”

European Journal of Preventive Cardiology

Arguryidou et al., 2020

MAIN POINT: “A simple self-reported measure of walking pace was the only lifestyle variable found to improve risk prediction for all-cause and cardiovascular mortality when added to established risk factors.”

“Wearable-device-measured physical activity and future health risk”

Nature Medicine, 2020

Strain, et al.

Why? Originates the PAEE calculations and MVPA/Vigorous standards

VOLUME \*AND\* INTENSITY MATTER

Goal: Used measured PAA and % MVPA as an exposure for all-cause mortality. Shows that BOTH OVERALL PHYSICAL ACTIVITY \*AND\* PA INTENSITY MATTER!!

Study Design: 96k inds in UK Biobank.

“The fraction of PAEE from MVPA was the sum of energy expenditure from activity above 3 METs divided by total PAEE, expressed as a percentage (Supplementary Table [7](https://www.nature.com/articles/s41591-020-1012-3#MOESM1)). MVPA time (minutes per day) was calculated directly from the original time variables for the intensity categories above 3 METs. Figure [1](https://www.nature.com/articles/s41591-020-1012-3#Fig1) presents an overview of the study methods. Two individuals were excluded whose values of PAEE were clearly outliers (>9 standard deviations from the mean; Extended Data Fig. [5](https://www.nature.com/articles/s41591-020-1012-3#Fig9)).”

“Our main analyses excluded 217 individuals who died in the first year of follow-up to minimize the risk of reverse causality”

Exposures:

Confounder Set: Took variables from time closest to accelerometer start date (except sex and Townsend Index, ethnicity). Age, sex ethnicity, Townsend Index, highest educ level achieved, employment status, season of accelerometer wear, alcohol drinking status, fruit and veggie intake, processed red meat intake, sleep duration. Possible MEDIATORS were blood pressure and cholesterol meds, mobility limits, BMI, prior condition.

Model Specification: Cox proportional hazards model w/ age as the timescale, used RESTRICTED CUBIC SPLINE W THREE EVENLY PLACED KNOTS

MVPA - This is generally considered a brisk walk.. METs score of >= 3. This translates to XXXX mg in accelerometer data

Results: “Higher PAEE was associated with a lower hazard of all-cause mortality for a constant fraction of MVPA. Similarly, a higher MVPA fraction was associated with a lower hazard when PAEE remained constant”

Results for Overall PA: “When considering the associations of PAEE alone (adjusting for all covariates but not the fraction of PAEE from MVPA), undertaking an additional 5 or 15 kJ kg−1 d−1 from a low baseline of 15 kJ kg−1 d−1 was associated with a 37% (95% confidence interval 27–46%) or 69% (59–77%) lower hazard of all-cause mortality, respectively (Fig. [2a](https://www.nature.com/articles/s41591-020-1012-3#Fig2) and Supplementary Table [3](https://www.nature.com/articles/s41591-020-1012-3#MOESM1)). The association was nonlinear, being steeper between 15 and 30 kJ kg−1 d−1, and then stabilizing around 80% lower hazard. “

Results for % MVPA: “ Accumulating 20% of PAEE from MVPA compared to 5% was associated with a 56% (24–75%) lower hazard, after adjustment for covariates and PAEE (Fig. [2b](https://www.nature.com/articles/s41591-020-1012-3#Fig2) and Supplementary Table [4](https://www.nature.com/articles/s41591-020-1012-3#MOESM1)). A 60% fraction was associated with a 91% (45–99%) lower hazard.”

RESULTS FOR INTERACTION: “In the interaction analyses of PAEE and the fraction of PAEE from MVPA, higher levels of both exposures were associated with lower hazard (Fig. [3](https://www.nature.com/articles/s41591-020-1012-3#Fig3) and Table [2](https://www.nature.com/articles/s41591-020-1012-3#Tab2)). All comparisons were made relative to 15 kJ kg−1 d−1 PAEE, with 10% from MVPA.”

Conclusions: “Our results show that higher volumes of PAEE are associated with reduced mortality rates, and achieving the **same volume through higher-intensity** activity is associated with greater reductions than through lower-intensity activity.”

FURTHER CONCLUSIONS FROM INCLUDING BOTH IN SAME REG: “Using data from the largest study including accelerometer-measured physical activity to date, we found that both higher total volume of PAEE and a higher fraction of PAEE accumulated in MVPA were associated with lower mortality rate. A moderately higher PAEE of 20 kJ kg−1 d−1 compared to 15 kJ kg−1 d−1 was associated with 21% lower premature mortality rate, when the fraction of MVPA was fixed at 10%. The difference between these scenarios is roughly equivalent to a 35-min stroll, with an extra 2 min at a brisker pace. A fixed PAEE of 15 kJ kg−1 d−1 but accumulating 20% rather than 10% from MVPA was associated with a 30% lower mortality rate—the equivalent of converting a 12-min stroll into a brisk 7-min walk. “

STRENGTHS:

“A major strength of this study, apart from its large sample size, is our method for anchoring the accelerometer-derived metrics of movement to the more easily interpretable scale of energy expenditure, using equations derived from combined heart rate and trunk acceleration sensors, validated in UK age-matched samples against the gold-standard criterion of doubly labeled water”

NO REVERSE CAUSALITY

Limitations??

“Limitations include our inability to make firm causal conclusions as our study is observational with physical activity measured at a single time point. Also, the intrinsic correlation between PAEE and the fraction of PAEE from MVPA means that joint results cannot be interpreted in its two constituent parts. Our analytical approach ensured that our results are not biased by statistical collinearity, but we have purposely avoided using the phrase ‘independent effects’ because of the inherent inter-dependence between the two exposures.

Another limitation is the unrepresentativeness of the sample, which may impact external validity. The main UK Biobank sample had a 5.5% response rate and has been shown to be healthier and more affluent than the general population[24](https://www.nature.com/articles/s41591-020-1012-3#ref-CR24). The accelerometer substudy was subject to further selection pressures (for example, survival five years after baseline, contacted by e-mail) that likely exacerbated some of these differences. However, our median value of PAEE of 40 kJ kg−1 d−1 is comparable with nationally representative age-specific estimates[25](https://www.nature.com/articles/s41591-020-1012-3#ref-CR25).

We considered intensity relative to overall absolute activity volume, although intensity relative to maximal capacity may be more critical to driving adaptations[26](https://www.nature.com/articles/s41591-020-1012-3#ref-CR26). However, we did adjust for mobility limitations that are associated with low physical capacity, and performed sensitivity analyses around the MVPA threshold and found similar results.

An intrinsic limitation to these data is that covariate measurement was not undertaken at the present study baseline (accelerometer mail-out) but at the physical visits to the UK Biobank assessment centers, a median of 5.7 years prior. Extended Data Figs. [2](https://www.nature.com/articles/s41591-020-1012-3#Fig6) and [3](https://www.nature.com/articles/s41591-020-1012-3#Fig7) show the change in covariates over this time period for the subsamples that undertook more than one assessment center visit. The responses are generally stable over time with the exception of medication use (for hypertension and high cholesterol) and employment status—indicators of health status and retirement, respectively. Our use of hospital episode statistics to identify prevalent disease status up until the present study baseline should identify the most serious cases of ill-health and mitigate some measurement error. The use of age as the underlying timescale may also reduce the residual confounding for inadequate measurement of both health and retirement status.”

ANOTHER POINT on PA INTENSITY NOT JUST OVERALL PA:

“Accelerometer-measured dose-response for physical activity, sedentary time, and mortality in US adults”

Am J Clinical Nutrition, Matthews et al., 2016

ANOTHER ONE:

“Volume of Light Versus Moderate‐to‐Vigorous Physical Activity: Similar Benefits for All‐Cause Mortality?”

AT SIMILAR VOLUME, MVPA associated with lower all-cause mortality than light PA

**Why is PA INTENSITY Important and not just overall PA?**

**“Physical activity volume, intensity, and incident cardiovascular disease”**

**European Heart Journal, 2022**

**Dempsey et al.**

**Implementation of volume and intensity w/ PAEE**

**Goal: Investigate role of PA intensity BEYOND its influence on total PA on incident CVD**

**Study Design: 88,412 UKB subjects in accelerometer cohort wearing accelerometers for 7 days on dominant hand - all WITHOUT prevalent CVD.**

**“**We have previously proposed an approach by simultaneously analysing PA volume and the proportion of that volume obtained through MVPA,[9](javascript:;) which honours the nested nature of intensity within volume.”

EXCLUDED PREVALENT CVD \*AND\* THOSE WHO EXPERIENCED CVD WITHIN 1 YEAR OF WEAR

**Confounders:**

**“**These models used age as the underlying timescale and modelled exposures using cubic splines with three evenly spaced knots. Exposure reference values were chosen as the nearest 5 kJ/kg/day or 5% to the first percentile of the distribution among those who had a CVD event.”

**Model: Cox PH model w/ PAEE and PAEE intensity (% MVPA)**

**Results:**

**“**Higher PAEE and higher %MVPA (adjusted for PAEE) were associated with lower rates of incident CVD. In interaction analyses, CVD rates were 14% (95% confidence interval: 5–23%) lower when MVPA accounted for 20% rather than 10% of 15 kJ/kg/d PAEE; equivalent to converting a 14 min stroll into a brisk 7 min walk. CVD rates did not differ significantly between values of PAEE when the %MVPA was fixed at 10%.”

**“**Interactions between PA volume and intensity were investigated by fitting a spline regression for PAEE and log-transformed %PAEE from MVPA, including interaction terms between the four orthogonal spline variables and %PAEE from MVPA. Using the coefficients, we plotted the fitted spline functions showing the association between PAEE and CVD risk for incremental fractions of PAEE from MVPA (10, 20, 30, and 40%). A 15 kJ/kg/day and 10% PAEE from MVPA reference was chosen for these models. Due to known differences in activity levels by sex in this cohort,[24](javascript:;) interaction analyses were also sex-stratified to investigate integrated volume/intensity associations for women and men separately.”

“In joint volume-intensity analyses, CVD rates were 14% (5–23%) lower when MVPA accounted for 20% rather than 10% of a fixed volume level of 15 kJ/kg/d PAEE ([*Figure 2*](javascript:;); [*Table 3*](javascript:;)). “

**Conclusions:**

**“**Reductions in CVD risk may be achievable through higher PA volume and intensity, with the role of moderately intense PA **appearing particularly important**.”

**“**This is equivalent to converting a 14-min stroll into a brisk 7-min walk; both have the same volume, but the higher intensity of the latter was associated with lower CVD rates “

Strengths & Limits:

Large sample size, validation of PAEE (and easily interpreted)

Residual bias, single time-point measured PA, not a representative cohort

**“Reallocation of time between device-measured movement behaviours and risk of incident cardiovascular disease”**

**Walmsley et al., 2022**

**Why? Used machine learning to better differentiate types of movement behaviors and risk of CVD in UK Biobank (another good estimate of risk based on PA intensity)**

**THEIR MAIN POINT: COMPOSITION of PA behaviors does not exist in a vacuum - getting more of one type of PA necessitates lowering other types**

**Methods: Developed machine learning model based on data from 152 individuals - MVPA, light PA, etc. w/ wrist-worn accelerometer data from UK Biobank**

**MODEL: COMPOSITIONAL data analysis Cox regression**

**Results: Reallocating 20 minutes/day to MVPA from all other behaviors proportionally associated w/ 9% lower risk (7 to 10% CI), while reallocating 1 hour/day to sedentary behavior increased risk 5%**

**\*\*\*\*\*NOTE: MEASURES MVPA SAME WAY AS WE DO (>= 3 METS) but DOES not that this cutoff technique is prone to misclassification…**

**IMPORTANCE OF PA INTENSITY IS ALSO ACKNOWLEDGE BY AHA and WHO STANDARDS:**

**“American Heart Association Recommendations for Physical Activity in Adults and Kids”**

**2018**

* Get at least **150 minutes per week** of moderate-intensity aerobic activity or 75 minutes per week of vigorous aerobic activity, or a combination of both, preferably spread throughout the week.
* Add moderate- to high-intensity muscle-strengthening activity (such as resistance or weights) on at least 2 days per week.
* Spend less time sitting. Even light-intensity activity can offset some of the risks of being sedentary.
* Gain even more benefits by being active at least 300 minutes (5 hours) per week.
* Increase amount and intensity gradually over time.

**“Global recommendations on physical activity for health” 2010, WHO**

**Conclusions:**

“1. Adults aged 18–64 should do at least 150 minutes of moderate-intensity aerobic physical activity throughout the week or do at least 75 minutes of vigorous-intensity aerobic physical activity throughout the week or an equivalent combination of moderate- and vigorous-intensity activity.

2. Aerobic activity should be performed in bouts of at least 10 minutes duration.

3. For additional health benefits, adults should increase their moderate-intensity aerobic physical activity to 300 minutes per week, or engage in 150 minutes of vigorous-intensity aerobic physical activity per week, or an equivalent combination of moderate- and vigorous-intensity activity.

4. Muscle-strengthening activities should be done involving major muscle groups on 2 or more days a week”

**EARLIER STUDIES SHOWING THE IMPORTANCE OF THIS DISTINCTION - Long-established**

**“A Prospective Study of Walking as Compared with Vigorous Exercise in the Prevention of Coronary Heart Disease in Women”**

**Manson et al., NEJM 1999**

**Goal: Role of walking versus vigorous exercise**

**Study Design: Prospective 8-year follow-up design**

**Conclusions: Shows clear benefits to both vigorous and brisk walking for reduced CHD incidence**

**“Exercise Type and Intensity in Relation to Coronary Heart Disease in Men”**

**Tanasescu et al., 2002, JAMA**

Goal: Investigate effect of exercise intensity on CHD incidence and mortality

Study Design: Prospective cohort

Conclusions: “Total physical activity, running, weight training, and walking were each associated with reduced CHD risk. Average exercise intensity was associated with reduced risk independent of the number of MET-hours spent in physical activity.”

“The Physical Activity Guidelines for Americans”, JAMA, Piercy, 2018

Conclusions:

“Adults should do at least 150 minutes to 300 minutes a week of moderate-intensity, or 75 minutes to 150 minutes a week of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate- and vigorous-intensity aerobic activity.”

“Individuals performing the least physical activity benefit most by even modest increases in moderate-to-vigorous physical activity.”

ALSO SOME MECHANISTIC EVIDENCE FOR IMPORTANCE OF PA INTENSITY:

“Integrative Biology of Exercise”,

Hawley, et al., Cell, 2014

Conclusions: Overview of existing literature and concludes in part that exercise intensity and capacity associated w/ cardiovascular disease mortality

“Importance of Assessing Cardiorespiratory Fitness in Clinical Practice: A Case for Fitness as a Clinical Vital Sign: A Scientific Statement From the American Heart Association”

Circulation, Ross et al., 2016

Conclusion:

“The underlying premise of this statement is that the addition of (cardiorespiratory fitness) CRF for risk classification presents health professionals with unique opportunities to improve patient management and to encourage lifestyle-based strategies designed to reduce cardiovascular risk.”

**FOR FURTHER DESCRIPTION OF DATA WE ARE MAKING USE OF:**

“Large Scale Population Assessment of Physical Activity Using Wrist Worn Accelerometers: The UK Biobank Study”

Doherty et al., 2017 PLOS ONE

Worn on dominant hand

“Participants were approached by email to wear a wrist-worn accelerometer for seven days that was posted to them. Physical activity information was extracted from 100Hz raw triaxial acceleration data after calibration, removal of gravity and sensor noise, and identification of wear / non-wear episodes. “

“103,712 datasets were received (44.8% response), with a median wear-time of 6.9 days (IQR:6.5–7.0). 96,600 participants (93.3%) provided valid data for physical activity analyses.”

“keep the data secure, and to use it only for the purposes of the approved research [[16](https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0169649#pone.0169649.ref016)]. Between February 2013 and December 2015, participants who had provided a valid email address were sent an email invitation to wear an accelerometer for seven days. The participant email addresses were chosen randomly, with the exception of the North West region which was excluded for much of the project due to participant burden concerns, as this area had been used to trial new projects. From June 2013, participants were sent devices in order of acceptance. This study was covered by the general ethical approval for UK Biobank studies from the NHS National Research Ethics Service on 17th June 2011 (Ref 11/NW/0382). None of the authors had direct contact with the study participants.”

Axivity AX3 wrist-worn triaxial accelerometer

“Briefly, we identified stationary periods in ten second windows where all three axes had a standard deviation of less than 13.0 mg. These stationary periods were then used to optimise the gain and offset for each axis (9 parameters) to fit a unit gravity sphere using ordinary least squares linear regression. If insufficient data were available to conduct calibration for a given participant (where any of the three sensor axes did not have values outside a +- 300 mg range), we used the calibration coefficients from the previous (or if unavailable, the next) accelerometer record from the same device worn by a different participant. Clipped values, which occur when the sensor’s dynamic range of +-8g is exceeded, were flagged before and after calibration. Recording errors and ‘interrupts’, which could have occurred for example if participants tried to plug their accelerometer device into a computer, were also logged. Valid data were then resampled to 100 Hz using linear interpolation, except for interrupts lasting longer than 5 seconds which were set to missing. We calculated the sample level Euclidean norm of the acceleration in x/y/z axes, and removed machine noise using a fourth order Butterworth low pass filter with a cutoff frequency of 20Hz. In order to separate out the activity-related component of the acceleration signal, we removed one gravitational unit from the vector magnitude, with remaining negative values truncated to zero”

“We removed non-wear time, defined as consecutive stationary episodes lasting for at least 60 minutes where all three axes had a standard deviation of less than 13.0 mg [[12](https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0169649#pone.0169649.ref012),[14](https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0169649#pone.0169649.ref014)]. We imputed non-wear data segments using the average of similar time-of-day vector magnitude and intensity distribution data points with one minute granularity on different days of the measurement, as in previous studies [[12](https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0169649#pone.0169649.ref012),[14](https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0169649#pone.0169649.ref014)]. This imputation accounts for potential wear time diurnal bias where, for example, if the device was systematically less worn during sleep in an individual, the crude average vector magnitude during wear time would be a biased overestimate of the true average.”

96,600 inds - again exact same as in ours before kinship screening!

…” illustrates that 80.6% of participants wore the device for at least 150 hours out of a scheduled 168 hours. Men wore the device for a median of 166.3 hours (IQR: 157.7–168.0) and were slightly more compliant than women who wore the device for a median of 165.6 hours (IQR: 156.7–167.0).”

***SOURCE TO CITE ABOUT WEAR TIME OF 4+ DAYS IN THE WEEK:***

***“Conducting accelerometer-based activity assessments in field-based research”***

***Point - 4 days of wear at least approximates week of activity well***

***Trost et al., 2005, Med Sci Sports Exercise***

**Why is OBJECTIVELY measured PA so important IN A POPULATION SAMPLE like UKB?**

**“Comparison of a Subjective and an Objective Measure of Physical Activity in a Population Sample”**

**Journal of Physical Activity and Health, Hagstromer, et al. 2010**

**Study Design: Comparing self-administered IPAQ - International Physical Activity Questionnaire (gold-standard for subjective PA - estimates in METs-minute) in a population-based sample (like UK Biobank). 980 subjects in Sweden wore accelerometer for 7 days then filled out IPAQ.**

**Note: Ages 18-65, so only some overlap w/ our sample’s age range…**

**On IPAQ (can be self- or professional-administered and based on 7 day recall):**

**27 items - duration and frequency of different tasks completed in a day**

**MET - Metabolic equivalent task**

**MVPA = 4 METs, vigorous = 8 METs**

**Walking = 3.3 METs**

**One MET = energy expenditure during rest - 1 kcal/kg/hr in adults**

**Conclusions: Correlation of IPAQ and accelerometer-measured PA was low to moderate (Spearman Rank Order Correlation Rs = 0.07 to 0.36) - and IPAQ has differential bias (higher values of IPAQ more prone to bias) - so IPAQ generally OVERESTIMATES PA… And correlation is weaker for women than men**

**“International Physical Activity Questionnaire (IPAQ) and New Zealand Physical Activity Questionnaire (NZPAQ): A doubly labelled water validation”**

**Maddison et al., 2007, Int J of Behavioral Nutrition and Physical Activity**

**Why this study? Shows that not only is there a large discrepancy between objective and subjective PA, but IPAQ also performs poorly relative to GOLD-STANDARD of DLW**

**Study Design: 36 adults aged 18-56 in New Zealand w/ DLW and 7-day IPAQ (and New Zealand-specific questionnaire)**

**Conclusions: on average relative to DLW, IPAQ \*underestimated\* activity-related energy expenditure at higher levels of PA… Off by 27% on average in IPAQ (compared to about 6% for accelerometer)**

**RANDOM - IMPORTANCE OF CALIBRATION IN ACCELEROMETER DATA (in UK-based population too)**

**“Autocalibration of accelerometer data for free-living physical activity assessment using local gravity and temperature: an evaluation on four continents”**

**Journal of Applied Physiology**

**Van Hees, et al., 2014**

**ANOTHER SOMEWHAT RANDOM - SHOWS DIFFICULTY OF USING STANDARDS (MORE USEFUL TO VIEW PA AS A SPECTRUM)**

**“Confusion and Conflict in Assessing the Physical Activity Status of Middle-Aged Men”**

**MAIN POINT: Depending on standard used, unclear whether males should be classified as physically active or not…**

**“Limits to the measurement of habitual physical activity by questionnaires”, BJSM, 2003**

“This uncertainty makes it difficult to convert epidemiological association results into public health recommendations about the minimum level of physical activity required for health and the benefits of engaging in different durations of activity of different intensity.”

Why this study? A more generalized critique of IPAQ

Study Design:

Conclusions: OTHER subjective PA difficulties: Trying to get a full accounting of PA BUT validity tends to be lower for longer surveys people must fill out

ALSO differences in, for instance, pace of walking…

ALSO desirability bias - overestimate frequency of positive activity, etc…

Higher level of measurement error overall (point made elsewhere too…)

“Are Self-report Measures Able to Define Individuals as Physically Active or Inactive?”

Steene-Johannssen, et al., Med Sci Sports Exercise, 2018

Study Design: Combined heart rate and movement sensing (“silver standard” for PA) measured at two time points for 1713 Europeans from 9 countries compared to IPAQ and other PA questionnaires.

IPAQ prone to OVERESTIMATE PA - only captured 20% of people who were insufficiently active according to accepted guidelines

Conclusions: Extremely low ability to assess PA (not sensitive to detecting physically inactive people) and V LOW level of agreement w/ objective PA (kappa = 0.07) - **AND SO RECOMMENDS USE OF OBJECTIVE MEASURES!!!**

**ALSO objective PA has STRONGER association w/ cardiometabolic RFs and CVD!!!**

STUDY SHOWING THAT IT IS INDEED THE “SILVER STANDARD”

“Validity of combining heart rate and uniaxial acceleration to measure free-living physical activity energy expenditure in young men”

Villars et al., 2012, Journal of Applied Physiology

ON GENERAL USEFULNESS OF ENMO (which is UKB base we use to calculate PAEE) - main point is adjusting for gravity improves performance…

“Separating Movement and Gravity Components in an Acceleration Signal and Implications for the Assessment of Human Daily Physical Activity”

PLOS One, van Hees, et al., 2013

“Association Between Questionnaire- and Accelerometer-Assessed Physical Activity: The Role of Sociodemographic Factors”

Sabia et al., AJE 2014

Why? Self-reported PA questionnaires are ALSO differentially biased by sociodemographic

Study Design: 3975 individuals from Whitehall II Study in the UK with participants aged 60-83

Conclusions: Moderate correlation of objective and questionnaire PA (r = 0.33) similar to previous studies but correlations were generally lower for people at lower levels of educational attainment and occupational status

ALSO SHOWS THAT THESE SAME CONCLUSIONS GENERALLY HOLD IN OLDER ADULT POPULATION (like in UKB)

“Prospective Associations of Accelerometer-Measured Physical Activity and Sedentary Time With Incident Cardiovascular Disease, Cancer, and All-Cause Mortality” (Research letter)

Dempsey et al., Circulation, 2020

Why? Just another data point for use of MVPA and Vigorous PA without step counts

Goal: Examine prospective association of accelerometer-measured PA w/ incident CVD (and cancer and all-cause mortality)

Study Design: Participants from EPIC-Norfolk study w/ 25k adults aged 40 to 79 wearing accelerometer on right hip for 7 days and used Cox regression

Exposures: Accelerometer-measured MVPA, light PA, sedentary time

Results:

“higher levels of total PA and MVPA were associated with lower incident CVD risk in a nonlinear manner; after an initially steeper decrease in hazard ratios, there was a flattening of the relationships”

LIKE OTHERS DID SENSITIVITY ANALYSIS - but by excluding those who died within first TWO YEARS of analysis

Conclusions: Relationship between lower incident CVD and higher MVPA that attenuates BUT this could be simply due to declining sample size at upper end of distribution

Strengths & Limits: PA was measured AT A SINGLE TIME POINT (ours too)

**“Physical activity intensity profiles associated with cardiometabolic risk in middle-aged to older men and women”**

Prev Med, 2022, Dempsey et al.

Why? PA \*intensity\* is important independent of total PA for cardiometabolic RFs in the same age group

Study Design: **Multivariate pattern analysis** of spectrum of PA intensity for 3660 middle to older aged adults from EPIC-Norfolk w/ UNIAXIAL accelerometer on right hip for data, sex-stratified

Partial Least Squares w/ Monte Carlo for resampling to validate - to find best fitting model (fit w/ a ton of PA intensity intervals at first)

DID BIVARIATE SPEARMAN RANK CORRELATION COEFF - SEEMS PRETTY STANDARD AS WELL

Confounders: Age, gender, education level, smoking status, alcohol intake, hypertension, diabetes at baseline, meds, habitual diet (pretty typical stuff)

Exposures: CMR Score was the outcome (waist, BP, lipids, glucose metabolism)

Results: HIGHER PA intensity does yield greater benefits… but also some benefits at lower than MVPA

Limits: SELECTION BIAS, limited ability to differentiate different activity types, possible reverse causation, imperfect diet measurement and residual confounding,

“Dose Response Between Physical Activity and Risk of Coronary Heart Disease: A Meta-Analysis”

Circulation, Sattelmair et al., 2011

Should give us insight on how we’re modeling this situation - AND show how much self-reported understates risk difference between physically active and inactive adults

Why? First review to look at specific amount of PA to lower CHD risk (previous used rough high/medium/low thresholds)

Model - RE generalized least squares spline models

“We used spline models to conduct GLST analyses for LTPA, which allowed the relation between physical activity and CHD to vary across the range of physical activity dose in kilocalories per week but assumed linear relations between designated doses.”

Results - Inds who engaged in 150 minutes/week of moderate intensity leisure-time PA had 14% lower risk compared to those who reported none - BUT 20% lower risk for those who met ADVANCED guidelines

ALSO NOTED THAT RISK RED WAS STRONGER FOR WOMEN THAN MEN (interaction by sex)

NOTE: NOT a very strong association but relying on SELF-REPORT HERE (IPAQ)

Conclusions - Some PA is better than none and additional benefits accrue with more PA

“Comparison of physical activity assessed using hip- and wrist-worn accelerometers”

Gait & Posture, Kamada, et al. 2016

**Where the MVPA and vigorous PA numbers were VALIDATED!!!**

“Feedback from physical activity monitors is not compatible with current recommendations: A recalibration study”

Prev Med

Why? Nice overview of why current PA standards are inaccurate for most people

INTRO - PA standards are based on getting PA IN ADDITION TO DAILY LIFE ACTIVITIES… Accelerometer captures ENTIRETY of PA (so 150 and 75 are ONLY add’l to what people usually get)… OW people will assume they are well over accelerometer targets…

Methods: Pooled data from 4 studies between 2006 and 2014 - FOUND AMOUNT OF MVPA for PAL of 1.75

Two different techniques: 1. Research instrument that used combined accelerometry measures and heart rate monitoring

CONCLUSION - Current physical activity standards are based on self-reported data, which poorly reflects how people generally get PA data these days (accelerometer-based)

Instead, they recommend roughly 1,000 minutes of MVPA activity per week (735 mins/week of MVPA as current median in study)

**OUR VIEW - THIS IS PART OF WHY DOSE-RESPONSE RELATIONSHIP IS SO IMPORTANT TO UNDERSTAND - RIGHT AMOUNT OF DIFF TYPES OF PA IN AGE OF ACCELEROMETERS IS NOT CLEAR…**

THEIR LOGIC FOR 3 METS:

“We have used an absolute threshold of 3 METs since this includes most forms of walking (Ainsworth et al., 2011) and is ubiquitous amongst most physical activity guidelines (Thompson et al., 2009). Whilst it would be theoretically possible to shift this MET threshold upwards to reduce the amount of reported activity to a level closer to 150 minutes a week, it would be inappropriate to meddle with what is meant by moderate intensity physical activity to try and force a fit with existing recommendations.”

“Confusion and Conflict in Assessing the Physical Activity Status of Middle-Aged Men”

PLOS One, Thompson et al., 2009

“2011 Compendium of Physical Activities: A Second Update of Codes and MET Values”

“Combined lifestyle factors, all-cause mortality and cardiovascular disease: a systematic review and meta-analysis of prospective cohort studies”

JECH, Zhang et al., 2020

Why? Good current overview on relationship of PA and CVD - DOES look at combined effect of healthy lifestyles, which is less useful than decomposition for our purposes. CAN ALSO SHOW RELATIVE IMPORTANCE OF PA COMPARED TO OTHER FACTORS IN LIFE’S SIMPLE 7!!!

Model: Systematic review and meta-analysis.

Lifestyle factors included: cigarette smoking, alcohol consumption, physical activity, diet, overweight/obesity, sleep duration and quality

Results: Combined healthy lifestyles reduced risk of incident CVD massively (HR = 0.38) - consistent across groups of different SES, different continents, different races

HR = 0.31 for incident CHD

“Life's Simple 7: Vital But Not Easy”

Sanchez, 2018, JAHA

Why? Editorial to stress that PA intensity is a PILLAR of heart disease prevention

“Healthy Lifestyle Factors in the Primary Prevention of Coronary Heart Disease Among Men: Benefits Among Users and Nonusers of Lipid-Lowering and Antihypertensive Medications”

Circulation, Chiuve et al., 2006

Why? Just another OG article - GIVES US A GOOD FIRST ESTIMATE OF EFFECT SIZE

Methods: Prospective cohort of Health Professionals (highly educated) Follow-Up Study ages 40-75 over 42k men

Biennial self-administered questionnaire

ALL measures were SELF-REPORTED and used Cox model

RFs: Diet, PA, managing weight, no smoking

**Exercise - low risk if 3.5+ hours/week - produced RR of 0.72 (exercise defined as 4+ METs)**

Results: RR = 0.13 (but using Cox model) - for those at low risk for ALL 5 RFs vs those who were not low risk for any

Conclusions: MAJORITY of CHD events are preventable w/ lifestyle modification

“Accelerometer measured physical activity and the incidence of cardiovascular disease: Evidence from the UK Biobank cohort study”

Ramakrishnan, et al., PLOS Med, 2021

Why? From the people leading the way in accelerometer measured PA in UK Biobank… Closely related to own topic

Methods: CUT 95th and 5th percentiles of exposure

Model: Restricted cubic spline

Results: Linear dose-response relationship for MVPA, vigorous, total PA volume

MVPA relative to lowest 4th: 0.71, 0.59, 0.46 HR

Total volume of PA: 0.73, 0.63, 0.47

***EXISTING GxE Studies Relevant to Our Topic:***

“Associations of Fitness, Physical Activity, Strength, and Genetic Risk with Cardiovascular Disease”

Circulation, Tikkanen, et al., 2018

Why? The scoopers… So clearly important to use to show existing relationships

Methods: Objective and subjective PA association w/ CVD in the UK Biobank are the key outcomes - ALSO looked at grip strength and cardiorespiratory fitness

502k inds in UK Biobank over median follow-up of 6.1 years

\*\*\*THEN stratified by genetic risk and looked at CVD/CHD/AFib

BROKE PA AND GENETIC RISK INTO TERTILES

Confounders:

Age, sex, region, ethnicity, Townsend Index, BMI, diabetes, lipid medication, blood pressure, height??

Used MICE TO IMPUTE MISSING VALUES

Cox PH Models (evaluated PH assumption via Schoenfeld residuals)

RANK TRANSFORMED PA MEASURES TO MAKE COMPARABLE

Results: HR = 0.95 per SD change in PA for incident CHD - RESULT BASICALLY HELD FOR INDS AT ALL LEVELS OF GENETIC RISK

Graphical user interface, application

Description automatically generated

Conclusions: Relatively weak overall - that PA reduces risk of incident CHD for inds of all genetic risk

STRONGER association or OBJECTIVE PA than for SUBJECTIVE PA

AND tells more about risk-modifying effects of PA for inds at different genetic risk

“In the longer term, identifying subgroups based on genetic risk that benefit most from lifestyle interventions could help personalize prevention strategies of chronic diseases.”

“The HR for the subjective measure of physical activity, IPAQ-PA, was notably more modest than that of the objective measurement (HR, 0.83; 95% CI, 0.82–0.84; [Table 4](https://www.ahajournals.org/doi/full/10.1161/CIRCULATIONAHA.117.032432#T3)) than the association of physical activity objectively measured by accelerometer. The correlation of these 2 measures was modest (*R*=0.20), indicating substantial measurement inaccuracy in self-reported physical activity.”

NO SIG DIFFERENCE BY TERTILE FOR INDS BY GENETIC RISK W IPAQ

Limitations:

ME - This study did NO screening for genetics besides screening out those who were not genotyped…. CAN CREATE SPURIOUS ASSOCATIONS BY ANCESTRY OR LOW GENOTYPING QUALITY!!!!

ONLY USED ACCELEROMETER DATA FOR ALL-CAUSE MORTALITY!!!!!

“Genetic Risk, Adherence to a Healthy Lifestyle, and Coronary Disease”

NEJM, Khera, et al. 2016

The OG here really

Why? Not just really the first to look at healthy lifestyle and genetics but ALSO tertiles/subjective PA, so this is what we’re improving from

Intro: Genetic risk and lifestyle factors both contribute to CAD risk but degree to which healthy lifestyle can offset genetic risk is unclear

Methods: In three prospective cohorts (ARIC, WGHS, and MDCS) and a cross-sectional study - w/ 55,685 participants in total, used a polygenic score and adherence to healthy lifestyle (no current smoking, no obesity, regular PA, healthy diet) to assess risk of CAD

PGS - 50 SNPs associated w/ risk of CAD at genome-wide significance

DEFINITION OF PA - Physical activity at least once weekly

Outcome: CAD (MI, coronary revascularization, death from coronary causes)

Confounders: age, sex, self-reported educational attainment, first five principal components of ancestry

Model: Cox PH model - Compared high genetic risk (top quintile) with intermediate risk (2 to 4), and low risk (lowest quintile)

MEASURE OF ASSOCATION: Did hazard ratios but ALSO 10-year event rates - standardized to mean of all predictor variables within each population

DID SAME SORT OF CLASSIFICATION FOR NUMBER OF HEALTHY LIFESTYLES

Results:

The relative risk of incident CAD was 91% higher among participants at high genetic risk (top quintile vs bottom quintile of genetic risk) than among those at low genetic risk (bottom quintile)

HR = 1.91 (95% CI: 1.75 to 2.09)

Favorable lifestyle (defined as at least 3 out of 4 healthy lifestyle indicators) was associated with far lower risk than unfavorable lifestyle (1 or fewer healthy lifestyle indicators)

MOST RELEVANT RESULTS:

Among participants at high genetic risk (top quintile), favorable lifestyle associated with 46% lower relative risk of CAD than unfavorable (HR = 0.54 CI = 0.47 to 0.63)

CORRESPONDS to reduction in standardized 10-year incidence of coronary events from 10.7% to 5.1% in ARIC, 4.6 to 2.0% in WGHS, and 8.2 to 5.3% in MDCS

NOTE:

Adherence to favorable lifestyle associated with 45% lower relative risk in low genetic risk group, 47% lower in intermediate group, and 46% in high genetic risk group

NATURALLY THIS MEANS LARGER REDUCTION IN ABSOLUTE RISK IN HIGHER RISK GROUPS…

ALSO advantages of LOW genetic risk largely offset by unfavorable lifestyle

DID NOTE SIMILAR FINDINGS IN BLACK POP (ALTHOUGH GENETIC RISK WAS NEVER VALIDATED IN THEM AND V SMALL SAMPLE)

Conclusions:

**Lifestyle and genetic risk had independent associations with CAD susceptibility. AMONG PARTICIPANTS AT HIGH GENETIC RISK, favorable lifestyle associated w/ nearly 50% lower relative risk than unfavorable lifestyle**

Limitations:

Adherence to healthy lifestyle is not random

Investigators in different cohorts used slightly different methods

Competing risks and behavioral changes before or after assessment

LIMITED NUMBER OF SNPS USED IN PGS

NEED MORE ROBUSTLY DIVERSE POP

“Genetic Risk, Muscle Strength, and Incident Stroke: Findings From the UK Biobank Study”

Mayo Clinic, Kim et al., 2021

Why? Good measure of how PA CAPACITY affects incidence of stroke (both at least somewhat related to our question)

Intro: Included 284,767 white British participants in UKB WITHOUT GENETIC RELATEDNESS or stroke/MI at baseline between March 13, 2006 and October 1, 2010

Methods: Assessed genetic risk w/ PRS, assessed muscular strength via grip strength tests, 11.5 year follow-up

Confounders: sex, BMI, smoking status, employment, Townsend, alcohol consumption, processed meat consumption, resting pulse rate (CRF), blood pressure, LDL, hypertension meds, MVPA, ALSO GENOTYPING ARRAY AND PRINCIPAL COMPONENTS

Model: Cox regression with age as time scale

Results: HR of stroke was 0.81 and 0.76 for middle and top tertiles of grip strength relative to bottom tertile after adjusting for confounders and genetic risk

Higher genetic risk independently associated w/ higher stroke risk

Stroke hazards for top muscle strength tertile were consistently lower across genetic risk strata, with no evidence of interaction

Compared w/ individuals w/ high muscle strength and low genetic risk, stroke hazards higher for individuals with medium or high genetic risk combined with low or medium strength but NOT for those w/ medium genetic risk and high muscle strength

Conclusion: Higher muscle strength was associated with lower risk of stroke incidence in all individuals regardless of genetic susceptibility. Increased genetic risk of overall stroke was partly attenuated through increased muscle strength

Limitations:

White British sample

NOT causal or physiological mechanism-based

Relatively small number of cases

“Genetic risk, incident stroke, and the benefits of adhering to a healthy lifestyle: cohort study of 306 473 UK Biobank participants”

BMJ, Rutten-Jacobs, et al., 2018

Why? ANOTHER study to base off of with different outcome but same general framework and IN UKB (SAME as other with pooled ‘lifestyle’ risk)

Intro: Oh so this is basically a CARBON COPY of the Mehta et al. study…

Genetic risk of stroke and lifestyle factors (non-smoker, healthy diet, BMI < 30, regular physical exercise) effect on stroke

Methods: UK Biobank w/ 306,473 men and women recruited from 2006 to 2010 - median follow-up time of 7.1 years.

GENETIC RISK SPLIT INTO THIRDS

Polygenic score - 90 independent SNPs that were previously associated with stroke at p<1x10^-5

Outcomes and exposures include IMPUTED GENETIC DATA, incident stroke, lifestyle

INCLUDE \*ONLY\* WHITE BRITISH INDIVIDUALS with COMPLETE VARIABLE INFO AND NO INCIDENT STROKE (restrictive)

DIFFERENCE: Defined physical activity as two or more bouts of moderate physical activity per week

Model: Cox proportional hazards - used time since baseline as time scale

Used COMPETING RISK MODEL and cumulative incidence function (used ‘survival’ and ‘cmprsk’ in R)

Confounders: Adjusted for age, sex, genetic PCA, and genotyping batch

INCLUDED AN INTERACTION TERM IN REGRESSION MODEL TO TEST FOR INTERACTION BETWEEN LIFESTYLE AND GENETIC RISK

Results:

2077 incident strokes over the time frame - risk was 35% higher among those at high genetic risk vs those at low genetic risk (top and bottom tertile) - HR = 1.35

Unfavorable lifestyle (defined identically as 1 or fewer lifestyle factors) increased risk of stroke 66% compared with favorable lifestyle (3+ lifestyle factors) HR = 1.66

ASSOCIATION with lifestyle was INDEPENDENT of genetic risk strata

HIGHEST hazard was for individuals at highest genetic risk and unfavorable lifestyle (2.30) relative to favorable and low genetic risk

Conclusions:

Genetic and lifestyle factors were independently associated with incident stroke - highlights benefits for entire population adhering to a healthy lifestyle independent of genetic risk

Limitations:

Strengths are large sample size, largest genome-wide association study to derive PGS

Behavioral changes before or after examinations would not be caught

Focused on a narrow range of lifestyle factors

MORE DETAILED ASSESSMENT OF PA WOULD BE OF INTEREST FOR FUTURE STUDIES

NOT generalizable

ALSO NICE OVERVEIW FROM PAPER ON IMPUTATION PROCESS:

We used the June 2017 release of the imputed genetic data from UK Biobank (downloaded 3 June 2017). Details of the design of the arrays, sample processing, and stringent quality control have been described in detail elsewhere[**12**](https://www.bmj.com/content/363/bmj.k4168#ref-12) and summarised previously.[**13**](https://www.bmj.com/content/363/bmj.k4168#ref-13) Briefly, we used two closely related arrays from Affymetrix, the UK BiLEVE Axiom array (9.9% of people) and the UK Biobank Axiom array, to genotype about 805 426 markers with good genome wide coverage. Phasing was performed using SHAPEIT3 and imputation using IMPUTE4.[**12**](https://www.bmj.com/content/363/bmj.k4168#ref-12)[**15**](https://www.bmj.com/content/363/bmj.k4168#ref-15) Two reference panels were used for imputation; the Haplotype Reference Consortium reference panel (39 131 578 autosomal single nucleotide polymorphisms, SNPs) and a merged UK10K and 1000 Genomes Phase 3 panel.[**14**](https://www.bmj.com/content/363/bmj.k4168#ref-14) Imputed genotypes were available for 488 369 participants in this study.[**12**](https://www.bmj.com/content/363/bmj.k4168#ref-12) From the resulting dataset, we excluded those who self reported ancestry other than white British, related people (second degree or greater: kinship coefficient ≥0.884), people with high levels of heterozygosity and missingness (>5%), and people whose reported sex was inconsistent with sex inferred from the genetic data. The UK Biobank core team centrally performed a check for excessive heterozygosity.[**13**](https://www.bmj.com/content/363/bmj.k4168#ref-13) Extreme heterozygosity or high rates of missingness, or both, can be indicators of poor sample quality due to, for example, DNA contamination. UK Biobank provided a list of samples with unusually high heterozygosity and we excluded those samples according to its recommendations. To evaluate a mismatch in sex self reported sex was compared with sex inferred from the genetic data (based on relative intensity of markers on the Y and X chromosomes). This sex mismatch evaluation was centrally performed by the UK Biobank core team and is described in detail elsewhere.[**12**](https://www.bmj.com/content/363/bmj.k4168#ref-12) This evaluation can be used as a way to detect sample mishandling or other kinds of clerical error. However, in a dataset of this size, some such mismatches would be expected owing to transgender people or instances of real (but rare) genetic variation, such as aneuploidies in sex chromosomes.

In this analysis we only included SNPs imputed from the Haplotype Reference Consortium panel.

(Part of that genetic susceptibility and healthy lifestyle cottage industry)

“Associations of genetic susceptibility and healthy lifestyle with incidence of coronary heart disease and stroke in individuals with hypertension”

European Journal of Preventive Cardiology, Wang et al., 2022

Why? Another study focused on lifestyle and PRS splitting and analysis

Intro: How genetic susceptibility and healthy lifestyle influence risk of incident CHD and stroke (in individuals w/ hypertension)

Methods: 258,531 European descendant subjects in the UK Biobank with hypertension at baseline

Polygenic scores - used 300 and 87 SNPs for scores for CHD and stroke, respectively - BROKEN INTO TERTILES

Lifestyle score - no obesity, no current smoking, regular PA, healthy diet

Model: Cox regression with age as underlying time scale, EXCLUDE first 2 years of follow up

Confounders: Sex, BMI, Townsend, smoking status, employment, alcohol consumption, sleep, household overcrowding, no car/home ownership, genotyping array, genetic principal components

Results:

Favorable lifestyle (3+ lifestyle components) associated with 37% lower hazard of CHD vs unfavorable (1 or fewer) at all levels of genetic risk

Evidence of interaction between genetics and lifestyle adherence WAS found for stroke (NOT for CHD)

Favorable lifestyle at high genetic risk had lower absolute risk of CHD or stroke compared to unfavorable lifestyle at low to intermediate genetic risk

Conclusions:

THE CONCLUSION IS SAME AS ABOVE - that healthy lifestyle was more protective than ideal genetic risk

Limitations:

Not causal

Self-reported exposure and confounders

Reverse causation

European so potentially not generalizable

“Genetic susceptibility, screen-based sedentary activities and incidence of coronary heart disease”

BMC Medicine, Kim et al., 2022

Why? ANOTHER of the genetic susceptibility type cottage industry but focused explicitly on screen time as exposure

Intro: Unclear whether association of screen-based sedentary activity and CHD varies by genetic susceptibility

Methods:

373,026 individuals of European ancestry in the UK Biobank without prevalent CHD

Genetic susceptibility - measured with weighted polygenic risk sore w/ 300 SNPs - AGAIN split into tertiles

Confounders: Sex, age, BMI, smoking status, employment status, Townsend, alcohol consumption, salt adding behavior, oily fish consumption, coffee intake, fruit and veggie intake, processed red meat, hypertension medication use, cholesterol med use, glucose lowering med use, sleep, MVPA/day via IPAQ, genotyping array, first 10 genetic principal components

Touch-screen questionnaires to assess TV viewing and computer use

Restricting to White Europeans and no missingness in covariates but NO GENETIC QC AS FAR AS I CAN TELL

Model: Cox regression w/ age as underlying time scale - ran separately for PRS and screen time, then as interaction, then as composite

Results:

Compared to at least 4 hours a day of TV viewing, HR of CHD was 0.84 and 0.94 for less than one hour and 2-3 hours per day adjusted for genetic risk and confounders

NO evidence of interaction between TV viewing and genetic risk

10.9% of CHD could be prevented if TV viewing were reduced to <= 1 hour per day (PAF - ASSUMING THIS IS CAUSAL..)

PAF values were relatively larger for medium and high genetic risk but confidence intervals overlapped

Conclusion:

Less TV viewing associated with lower CHD risk independent of genetic risk

Limitations:

Not causal

Recall bias and measurement error in exposures

UK Biobank biased toward healthier individuals than average in UK

“Associations of Combined Genetic and Lifestyle Risks With Incident Cardiovascular Disease and Diabetes in the UK Biobank Study”

JAMA Cardiology, Said et al., 2018

Why? ANOTHER in this cottage industry FROM JAMA CARD and with UK Biobank

Intro: Are poor combined health behaviors associated with risk of incident CVD and diabetes equally between individuals of low/intermediate/high genetic risk?

Methods:

339,003 individuals in the UK Biobank (White European and unrelated)

Genetic risk was categorized into QUINTILES

Lifestyle broken up as ideal/intermediate/poor - again based on smoking, BMI, PA, diet - Ideal if 3+, poor if 3+ POOR, intermediate o.w.

REFERENCE GROUP - Low genetic risk and ideal lifestyle

Model: Cox model

Confounders: Age, sex, genotyping array, first 30 principal components, years of education, Townsend, income

Results:

Genetic risk and lifestyle were independent predictors of incident events and NO INTERACTIONS

Compared with REF GROUP, poor lifestyle associated with 4.54 HR in the high genetic risk group

Conclusion:

Genetics and health behaviors had a LOG ADDITIVE (me - due to cox model presumably) effect on risk of CVD - The relative effects of poor lifestyle were comparable between genetic risk groups

Limitations:

NOT causal

Potential pleiotropy from SNPs

Data is SELF-REPORTED so measurement error

White British descent only

Did not take into account CHANGES in variables over time

“Finally, as increasingly more genetic variants are identified,51 the variance explained by genetics and GR estimates will improve. Similarly, improved monitoring of lifestyle factors, eg, physical activity, will allow more accurate risk estimates for lifestyle.”

“Polygenic Risk, Midlife Life's Simple 7, and Lifetime Risk of Stroke”

JAHA, Thomas et al., 2022

Why? Same TYPE of study as others but does differ in general approach (and most recent reviewed here)

Intro: Exploring how lifetime risk of stroke differs by level of genetic risk and the degree to which optimal lifestyle can offset high genetic risk of stroke

Methods:

11,568 middle-aged adults (23% black) followed up for median of 28 years(!!) - used ARIC

INNOVATIONS - ACTUALLY look at black individuals AND USES A PREVIOUSLY EXISTING PRS WITH MILLIONS OF VARIANTS

Lifestyle risk - ideal if 5-7 components, intermediate if 3-4, poor if 2 or fewer

Used AVERAGE category as reference group

MODEL - Used a modified survival analysis technique that ADJUSTS for competing risk of death and therefore provides actual risk of stroke in one’s lifetime

ALSO assessed using Fine and Gray proportional hazards models accounting for death as competing risk

STRATIFIED by PRS and LS7 category separately and calculated at ages 45/55/65/76/85

Confounders: sex, race, field center, education level, parental history of stroke

Results:

High PRS associated with 2.2x greater risk of stroke vs 40% lower risk of developing stroke in low genetic risk group (compared to intermediate)

NO interaction between genetic risk and LS7 adherence

Lifetime genetic risk of stroke at age 45 was 23.2% in high genetic risk vs 9.6% in low genetic risk

With BOTH high genetic risk and inadequate Life’s Simple 7 generated lifetime risk of 24.8%

ACROSS genetic risk groups, those with optimal LS7 had 30 to 43% lower lifetime risk than those with inadequate LS7 (almost 6 additional years lived free of stroke)

Conclusion:

Maintaining healthy habits can partially offset high genetic risk

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“Gene-Environment Interactions for Cardiovascular Disease”

Current Atherosclerosis Reports, Hartiala, et al., 2021

Just a good overview of existing GxE studies to that point - BUT given that it’s about INTERACTIONS it is related to the null results part of our paper mostly…

GxE Interaction - combined effect of genotype and exposure differs significantly from additive effects of genotype and exposure

IMPORTANT NOTE: ONLY REALLY ONE GxE w/ PA - LIKELY DUE TO GENERAL LACK OF STAT POWER TO DETECT AN INTERACTION EFFECT

“Self-reported walking pace, polygenic risk scores and risk of coronary artery disease in UK biobank”

NMCD, 2022, Zaccardi et al.

Why? HELPS show the potential importance of pace of exercise in addition to volume in driving CAD risk in this population

Methods: Another in the genetic/lifestyle risk cottage industry… Questionnaire “How would you describe your usual walking pace?”

DEFINED high genetic risk as top 20% of PGS distribution, moderate to low as bottom 80% (DICHOTOMIZED)

Results: Self-reported slow walkers w/ high genetic risk had highest risk of CAD

Risk difference between slow and brisk walkers was HIGHEST at HIGH genetic risk

NOTE: AND STRONG INCREASED RISK AMONG MEN WITH THESE FACTORS RELATIVE TO WOMEN…

STRATIFIED BY SEX

Found interactions between SOME PGS’s and self-reported walking pace

**Limitations of approach using accelerometer and cross-sectional PA - have some references in this category:**

Association of Changes in Physical Activity and Adiposity With Mortality and Incidence of Cardiovascular Disease: Longitudinal Findings From the UK Biobank

Mayo Clinic Proceedings, Ahmadi et al., 2018

MAIN POINT: Snapshot is insufficient for PA, as HR for individuals who met PA guidelines at both time points was similar to those who missed first but made second

**ADDING SOURCE FOR DRAWBACK OF USING ACCELEROMETER DATA:**

Ham SA, Reis JP, Strath SJ, Dubose KD, Ainsworth BE. Discrepancies between Methods of Identifying Objectively Determined Physical Activity. Med Sci Sports Exerc. 2007;39:52–58.

**“Further, activities reported in IPAQ such as heavy manual work, household scores, bicycling and weight lifting are not possible to capture with the accelerometer as the Actigraph only captures locomotor activities.”**

ANOTHER SOURCE PROVIDED BY LIA ON THIS SUBJECT…

“Pitfalls in accelerometer-based measurement of physical activity: The presence of reactivity in an adult population”

Scand J Med Sci Sports, Baumann et al., 2018

MAIN POINT: When people are being monitored, they tend to change behavior (at least over short term)

RESULTS: Wear time and light physical activity declined over the course of 7 days… HOWEVER, MVPA DID NOT!!!

ME - BUT WE HAD A SAMPLE WITH EXTREMELY HIGH LEVELS OF WEAR TIME COMPLIANCE!!!

***PRS Development:***

“Integration of questionnaire-based risk factors improves polygenic risk scores for human coronary heart disease and type 2 diabetes”

*Communications Biology*

Tamlander et al., 2022

SHORT OVERVIEW OF PGS CONSTRUCTION PROCESS FOR TAMLANDER:

Trained on the FinnGen study (n = 309,154) and validated on the UK Biobank (avoids winner’s curse bias)

The highest performing PGS for CAD that exists in the literature

Process:

Obtained weights from the largest GWAS on European-ancestry individuals that did NOT include UKB

Use PRS-CS to build genome-wise PRS’s - input weights came from a large GWAS independent of UKB - FINAL variant count of 1,089,342 (UNLIKE OTHERS, DO NOT CUT OFF AT GENOME-WIDE SIG… Improved performance this way)

Dropped samples with ambiguous gender, high genotype missingness, excess heterozygosity, non-Euro ancestry, all variants with minor allele count < 3 (DIVERGENCE - we remove all MAF < 1%... Minimal diff)

UK Biobank:

Phased and imputed centrally using Haplotype Reference Consortium merged with UK10k and 1000 Genomes phase 3 reference panels

PGS Catalog Ref:

“The Polygenic Score Catalog as an open database for reproducibility and systematic evaluation”

Lambert et al., 2021

Used the Polygenic Score Catalog, a resource that provides the variants/alleles/weights of existing polygenic scores and necessary metadata to replicate this PGS…

“Genome-wide risk prediction of common diseases across ancestries in one million people”

Mars et al., 2022

Cell Genomics

USED THIS ARTICLE (thru PGS Catalog) TO CREATE PRS!!!

ARTICLE ON IMPORTANCE OF CAD:

CAD is one of the leading causes of death and disability worldwide - AND has strong lifestyle and genetic components….

SOURCE:  
“Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015”

“Global, regional, and national disability-adjusted life-years (DALYs) for 315 diseases and injuries and healthy life expectancy (HALE), 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015”

RANDOM - JUST ANOTHER STUDY THAT USES MG CUTOFFS FOR MVPA AND VIGOROUS PA

“Prospective Associations of Accelerometer‐Assessed Physical Activity With Mortality and Incidence of Cardiovascular Disease Among Adults With Hypertension: The UK Biobank Study”

“Accelerometer-measured dose-response for physical activity, sedentary time, and mortality in US adults”  
THIS IS WHERE TRIMMING STARTED - did 1st and 99th percentile due to disproportionate influence on results (sparsity)

**RELATED - LIST OF STUDIES SHOWING STRONG GENETIC COMPONENT TO CAD:**

“Association analyses based on false discovery rate implicate new loci for coronary artery disease”

Nelson et al., 2017, Nature Genetics

“Population-specific and trans-ancestry genome-wide analyses identify distinct and shared genetic risk loci for coronary artery disease”

Koyama et al., 2020

“A comprehensive 1000 Genomes–based genome-wide association meta-analysis of coronary artery disease”

theCARDIoGRAMplusC4D Consortium, Nature Genetics, 2020

“Genetic risk and its role in primary prevention of CAD” - Roberts, et al., Journal of Translational Genetics and Genomics - ABOUT 50% GENETIC

ALSO CITE TAMLANDER AND MARS HERE

“Genetic Risk Stratification: A Paradigm Shift in Prevention of Coronary Artery Disease”

Roberts et al., 2021, JACC: Basic to Translational Science

POINT WITH ALL OF THESE: Genetics have a strong impact on an individual’s susceptibility to CAD and recent GWAS’s and polygenic scores have identified (hundreds of genome-wide sig and millions of variants) associated with risk - will likely continue expanding and improving performance as sample size and ability to detect rare variants improves…

**RELATED - LIST OF STUDIES SHOWING STRONG IMPORTANCE OF LIFESTYLE/PA:**

“Primary Prevention of Coronary Heart Disease in Women through Diet and Lifestyle”

Stampfer et al., 2000

Specifically shows that smoking, BMI, alcohol consumption, MVPA FOR AT LEAST 30 MINS PER DAY ALL INDEP ASSOC W LOWER CAD

“Ideal Cardiovascular Health: Associations With Biomarkers and Subclinical Disease and Impact on Incidence of Cardiovascular Disease in the Framingham Offspring Study”

Xanthakis et al., Circulation, 2014

Why? JUST another foundational study that shows importance of lifestyle (BMI, PA, etc.) for both subclinical disease and CVD

“Healthy Lifestyle in the Primordial Prevention of Cardiovascular Disease Among Young Women”

Chomistek et al., 2015, JACC

Why? Shows PA, normal BMI, etc. associated INDEPENDENTLY with reduced risk of CVD

“Low-Risk Diet and Lifestyle Habits in the Primary Prevention of Myocardial Infarction in Men: A Population-Based Prospective Cohort Study”

JACC, Akesson et al., 2014

Why? SHOWS that diet and PA COMBINE to reduce risk in a similar cohort (Swedish men ages 45 to 79) - based on self-report…

**POINT WITH ALL OF THESE (AND earlier studies…) - LIFESTYLE FACTORS (ESP PA VOLUME AND INTENSITY) HAS A MASSIVE IMPACT ON CAD RISK**

**NEED TO CITE MY DIRECT REF TO UK BIOBANK (same as in other article):**

“The UK Biobank resource with deep phenotyping and genomic data”

Bycroft et al., 2018

Nature

Coding Resources: (Used or Not):

<https://github.com/privefl/paper-ldpred2/tree/master/code> (Not Used... Likely need for PRS)

“LDpred2: better, faster, stronger” - Associated article for ldpred2

<https://privefl.github.io/bigsnpr/articles/LDpred2.html> - MORE OFFICIAL PRESENTATION ON LDPRED IN R

<https://github.com/getian107/PRScs> (Not Used - PRS-CS - common way of making PRS’s that uses python)

<https://github.com/Genomicsplc/ukb-pret> (NOT Used - allows comp of PRS performance FIT THRU UKB)

<https://www.pgscatalog.org/score/PGS002244/#PSS009521> - Used EXTENSIVELY to get scoring sheets

<https://github.com/kenhanscombe/ukbtools/blob/master/R/genetics_qc.R> (Not Used - a bit on QC in UKB… Trying to get kinship coefficients)

<https://github.com/OxWearables/rap_wearables/blob/main/2_Further_Prep_in_R.ipynb> (Used and MASSIVELY helpful for both accelerometer and overall data processing)

<https://github.com/dnanexus/OpenBio/tree/master/UKB_notebooks> (Used to get base code for data processing - WEBINAR ON NOV 2 WAS MORE USEFUL)

<https://github.com/ninamars/INTERVENE-PRS-transferability/blob/main/prs_calculation.sh> (Used - Code from MARS et al. on PRS)

<https://github.com/PGScatalog/pgsc_calc> (PGSCatalog Github - Tried to use…)

<https://www.medrxiv.org/content/10.1101/2022.06.16.22276246v2.full-text> (On release of PRS’s in UKB… Would’ve been nice…)

FURTHER NOTES ON OUR STUDY:

Overall acceleration here is Euclidean Norm Minus One (ENMO) - “The raw triaxial wrist acceleration data was auto-calibrated to local gravitational acceleration (in g) using a method described elsewhere [19]. The calibrated acceleration was then used to calculate Vector Magnitude (VM) per sample: ”

NEED TO \*ADJUST\* FOR NON-WEAR TIME - Right now have simply filtered out individuals w/ 3+ days of non-wear…

Per Doherty “We removed non-wear time, defined as consecutive stationary episodes lasting for at least 60 minutes where all three axes had a standard deviation of less than 13.0 mg [[12](https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0169649#pone.0169649.ref012),[14](https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0169649#pone.0169649.ref014)]. We imputed non-wear data segments using the average of similar time-of-day vector magnitude and intensity distribution data points with one minute granularity on different days of the measurement, as in previous studies [[12](https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0169649#pone.0169649.ref012),[14](https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0169649#pone.0169649.ref014)]. This imputation accounts for potential wear time diurnal bias where, for example, if the device was systematically less worn during sleep in an individual, the crude average vector magnitude during wear time would be a biased overestimate of the true average.”

LARGEST STUDY OF ACCELEROMETER-MEASURED PA THAT EXISTS

GOOD OVERVIEW ON UKB PROCESS FROM NATURE MEDICINE:

“Participants were instructed to wear a triaxial accelerometer (AX3, Axivity) on their dominant wrist for seven consecutive days, at all times, including swimming, bathing and sleeping. Raw acceleration was collected at 100 Hz resolution, calibrated to local gravity whilst also taking into account ambient temperature[30](https://www.nature.com/articles/s41591-020-1012-3#ref-CR30). This involves selecting periods of non-movement in individual data records (standard deviation <13m*g* in all three axes) as the vector magnitude (Euclidean norm) at that point should be 1*g*. The nine calibration parameters that influence deviation from this were optimized using an iterative procedure. This was carried out for each individual; if an individual did not have sufficient non-movement periods from which to calibrate, calibrations were taken from the measurements obtained from the subsequent user of the same device.

The Euclidean norm of calibrated acceleration in the three axes was calculated after removing machine noise using a fourth-order Butterworth low-pass filter at 20 Hz. From this, 1*g* was subtracted and any negative values were truncated to zero. As done previously, we denote this measure Euclidean norm minus one[31](https://www.nature.com/articles/s41591-020-1012-3#ref-CR31).

Non-wear time was considered to be time periods of ≥60 min where the standard deviation of acceleration in each of the three axes was <13 mg (ref. [32](https://www.nature.com/articles/s41591-020-1012-3#ref-CR32)). Missing data due to non-wear time were imputed on the basis of similar time-of-day segments from that individual.”

Table

Description automatically generated

“We used data from UK Biobank (application #33266), a population-based prospective cohort study of over 500 000 adults aged 40–69 years, recruited between 2006 and 2010 from across the UK. Methods have been described in detail previously.[23](javascript:;) In brief, a sub-sample of 103 686 participants responded to an email for the accelerometer sub-study between June 2013 and December 2015, with PA measurement a median of 5.3 years after their recruitment into the main study.[24](javascript:;) The UK Biobank study received ethical approval from the Northwest England Research Ethics Committee (reference 16/NW/0274). Participants gave informed consent before participation.”

“Accelerometry subsample participants were asked to wear a triaxial accelerometer (AX3, Axivity, UK) on their dominant wrist continuously (24 h/day) for 7 consecutive days. Measured acceleration from this type of sensor contains three main components: movement-related acceleration, gravity, and noise. A movement metric (Euclidean norm minus one, ENMO) was generated by calibrating measured wrist acceleration to local gravity (within the +/−1 g range and assuming sensor linearity to +/−8 g), filtering out sensor noise as a high-frequency signal component, and subtracting gravity.[25](javascript:;),[26](javascript:;) Non-wear was quantified as time periods of ≥60 min where the standard deviation of acceleration in each of the three axes was <13 mg, which was taken into consideration to minimize diurnal bias when summarizing the 5-s epoch time-series to average movement volume and distribution of intensity.[25](javascript:;),[26](javascript:;) The average ENMO over 5-s epochs (the intensity time-series) was summarized into average proportions of daily time spent at different movement intensity levels.[24](javascript:;) “