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ORIGINAL RESEARCH

Association of Habitual Physical Activity With Cardiovascular Disease Risk

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RATIONALE: A sedentary lifestyle is associated with increased risk for cardiovascular disease (CVD). Smartwatches enable accurate daily activity monitoring for physical activity measurement and intervention. Few studies, however, have examined physical activity measures from smartwatches in relation to traditional risk factors associated with future risk for CVD.

OBJECTIVE: To investigate the association of habitual physical activity measured by smartwatch with predicted CVD risk in adults.

METHODS AND RESULTS: We enrolled consenting FHS (Framingham Heart Study) participants in an ongoing eFHS (electronic Framingham Heart Study) at the time of their FHS research center examination. We provided participants with a smartwatch (Apple Watch Series 0) and instructed them to wear it daily, which measured their habitual physical activity as the average daily step count. We estimated the 10-year predicted risk of CVD using the American College of Cardiology/American Heart Association 2013 pooled cohort risk equation. We estimated the association between physical activity and predicted risk of CVD using linear mixed effects models adjusting for age, sex, wear time, and familial structure. Our study included 903 eFHS participants (mean age 53±9 years, 61% women, 9% non-White) who wore the smartwatch ≥5 hours per day for ≥30 days. Median daily step count was similar among men (7202 with interquartile range 3619) and women (7260 with interquartile range 3068; P=0.52). Average 10-year predicted CVD risk was 4.5% (interquartile range, 6.1%) for men and 1.2% (interquartile range, 2.2%) for women (P=1.3×10^{-26}). Every 1000 steps higher habitual physical activity was associated with 0.18% lower predicted CVD risk (P=3.2×10^{-4}). The association was attenuated but remained significant after further adjustment for body mass index (P=0.01).

CONCLUSIONS: In this community-based sample of adults, higher daily physical activity measured by a study smartwatch was associated with lower predicted risk of CVD. Future research should examine the longitudinal association of prospectively measured daily activity and incident CVD.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: adult ■ body mass index ■ exercise ■ primary prevention ■ risk factor

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Several observational studies support the association of physical activity with lower risk of cardiovascular diseases (CVDs) and mortality.[1–9] The current activity guidelines recommend at least 150 minutes of moderate to vigorous-intensity physical activity every week.[10] However, most adults spend most of their awake active hours performing light physical activities, such as walking, and this may represent an additional target for health promotion. A target of 10 000 steps per day is a commonly acknowledged target for physical activity,[11]

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Novelty and Significance

What Is Known?

- The current activity guidelines recommend at least 150 minutes of moderate to vigorous-intensity physical activity every week.
- A target of 10 000 steps per day is a commonly acknowledged target for physical activity.
- Measurement of habitual physical activity remains challenging and relation to outcomes remain lacking.

What New Information Does This Article Contribute?

- We examined the pattern of habitual physical activity measured by a study smartwatch in 903 participants.
- Every 1000 steps higher habitual physical activity was associated with 0.18% lower predicted risk of cardiovascular disease.
- The association was attenuated but remained significant after further adjustment for body mass index.

Regular physical activity has been recommended to improve heart health, but measurement of habitual physical activity remains challenging and relation to outcomes remain lacking. We examined the pattern of habitual physical activity measured by a study smartwatch. The study included 903 participants enrolled in the eFHS (electronic Framingham Heart Study). We found that every 1000 steps higher habitual physical activity was associated with 0.18% lower predicted risk of cardiovascular disease. The association was attenuated but remained significant after further adjustment for body mass index. Our study confirmed that higher daily physical activity measured by a study smartwatch was associated with lower predicted risk of cardiovascular disease in this community-based sample of adults.

Nonstandard Abbreviations and Acronyms

BMI	body mass index
BP	blood pressure
CVD	cardiovascular disease
eFHS	electronic Framingham Heart Study
FHS	Framingham Heart Study
IQR	interquartile range
PAI	physical activity index

but measurement of habitual physical activity remains challenging and relation to outcomes remain lacking. The standard physical activity questionnaires perform poorly at quantifying light physical activity.[12,13] To that end, several studies have leveraged short-term deployment of accelerometers and have reported protective effects from light physical activity and total step count, beyond what can be attributed to moderate to vigorous physical activity.[14–16] However, the methodology of prior studies using accelerometers carry risks of potential bias since most study accelerometers are only worn for short periods.[17,18]

Over the last decade, consumer-level wearable activity trackers have gained traction as powerful tools to monitor habitual physical activity. To the best of our knowledge, no prior studies have leveraged the abundant data collected by consumer-level wearable activity trackers to study them in the relation to clinical risk of CVD. The eFHS (electronic Framingham Heart Study) cohort was recently developed to add new mobile and digital phenotypes into the rich FHS (Framingham Heart Study) and leverage its deep CVD risk factor phenotyping, longitudinal follow-up, and established relationships with its participants.[19]

The objective of our current study is 2-fold: (1) to examine the pattern of habitual physical activity measured by a study smartwatch among eFHS participants and (2) to test the association of physical activity with the 10-year predicted CVD risk.

METHODS

The data that support the findings of this study will be available at BioLINCC https://biolincc.nhlbi.nih.gov/home/.

FHS is a community-based cohort, originally designed to study CVD and its risk factors.[20] Three generations of participants have been enrolled since 1948. In addition, spouses and multiracial Omni cohorts have been enrolled. The eFHS cohort was developed leveraging participants from the FHS Third Generation Cohort (Gen 3), multiethnic Omni Group 2 Cohort (Omni 2), and New Offspring Spouse Cohort, who are examined every 6 to 8 years.[19] The participants were invited to join in the eFHS during their regular research center examination (examination 3) and the enrollment began on June 27, 2016, with a smartphone app and a digital blood pressure (BP) cuff for home BP monitoring. Starting November 17, 2016, a smartwatch (Apple Watch, Generation 0)[21] was added to eFHS for daily activity and heart rate monitoring. Participants were also allowed to wear their own Apple Watch. To be eligible for the BP cuff and Apple Watch, the participants were required to own an iPhone with a compatible iOS (version 9 or higher). The FHS was approved by the Institutional Review Boards of Boston University Medical Center, and all participants provided written informed consent.

For the present study, we included the eFHS participants who received the study Apple Watch between June 27, 2016

and January 31, 2019. The participants were advised to wear the watch every day. Hourly step count data were stored on the participant's mobile device and transmitted to a secure cloud server regularly, which was later transferred to the FHS Research Center servers. Daily physical activity was quantified as the cumulative sum of hourly step count. Habitual physical activity was then calculated by the total number of steps divided by the total number of days with counts. In Figure 1, we depict the cohort development diagram for the current study. Of 3521 participants seen in the research center, 1948 were enrolled in the eFHS cohort. Among them, 705 participants had incompatible Android phones or declined to take the Apple watch, and 58 participants took the watch but did not send back data. A total of 1185 participants returned the step data.

To reduce bias because of no or low smartwatch wear time, valid study days were defined as the days in which participants had wear times of at least 5 hours during the day. In previous studies that deployed accelerometers to measure physical activity over short periods of time, an arbitrary threshold of 10 hours of wear time was used to define valid days.[14,15,22] We, however, chose a lower threshold to maximize the generalizability of our findings and avoid any exclusions related to the battery-life of the study smartwatch. Unlike accelerometers, validated algorithms for defining the wear time are not available for long-term wearable activity monitors. In the current study, we leveraged heart rate data from the study smartwatch to ensure the accuracy of wear time. The Apple Watch measures heart rate by photoplethysmography every 10 minutes at rest (more frequently during active hours).[23] Any clock hours with >1 heart rate recording were automatically counted in the wear time. For the hours where ≤1 heart rate recording was available, we only included hours with ≥30 recorded steps into wear time. The participants with <30 valid study days were excluded from downstream analyses (n=244, Figure 1).

For estimation of 10-year predicted CVD risk, we leveraged the American College of Cardiology/American Heart Association pooled cohort risk estimator.[24] The score is calculated using age, sex, race, total cholesterol, high-density lipoprotein cholesterol, BP, diabetes mellitus, smoking status, and treatment for hypertension. Demographic, clinical, and laboratory variables were measured during the Research Center examination.[20] Hypertension was defined as systolic BP ≥140 mm Hg and/or diastolic BP ≥90 mm Hg and/or self-reported use of antihypertensive medications. Diabetes mellitus was defined as fasting plasma glucose ≥126 mg/dL and/or self-reported use of medications for diabetes mellitus. Participants who had prior CVD or missing risk score (n=38; Figure 1) were excluded. Self-reported physical activity was estimated using the physical activity index (PAI) questionnaire administered during the Research Center examination for each participant.[25] PAI is a composite score calculated by summing up the products of hours at each level of activity times a weight based on oxygen consumption required for the activity. Different weights were assigned to each type of activity, including sleeping time (weight=1), sedentary time (weight=1.1), slight activity time (weight=1.5), moderate activity (weight=2.4), and heavy activity (weight=5).

Statistical Methods

Baseline variables of participants at the research center examination were presented as mean±SD for continuous variables, and frequency (proportion) for categorical variables. For comparison of continuous variables, we used Wilcoxon Rank-Sum test and for categorical variables, we used the Fisher exact test. We reported average daily step count and watch wear time as median (interquartile range [IQR]). We compared the average physical activity performed during weekdays (Monday

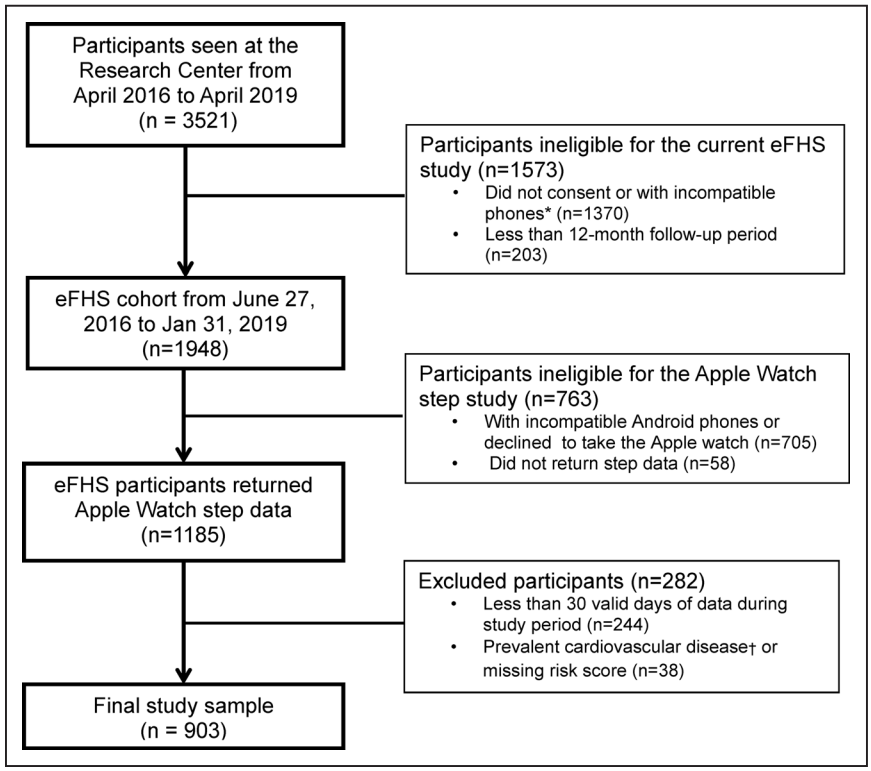

Figure 1. Cohort development diagram for study.
eFHS indicates electronic Framingham Heart Study. *Any iPhone with iOS 9 or higher was considered compatible. †Prevalent cardiovascular disease was defined as the history of myocardial infarction or stroke.

to Friday) to weekends (Saturday and Sunday). The correlation between the PAI and daily step count was measured using Pearson correlation coefficient. We stratified all analyses by sex and compared the predicted CVD risk and daily step count between men and women.

Linear mixed effects regression models were used to study the association between average daily step count (predictor variable) and predicted 10-year CVD risk (dependent variable). The model 1 was adjusted for age, sex, wear time, and familial structure/relatedness in FHS. Model 2 was further adjusted for body mass index (BMI), whereas model 3 additionally adjusted for hypertension, dyslipidemia, and diabetes mellitus. Covariates including age, sex, wear time, and BMI were treated as fixed effects, and familial relatedness was treated as the random effect, which was derived from the self-reported pedigree structure by R package kinship2. These variables were chosen a priori based on previously demonstrated association with measured physical activity.[26] Adjustment for the (watch) wear time has also been performed in previous studies using accelerometer data.

In secondary analyses, we studied reverse directionality of the association using linear mixed effects regression models with CVD risk as the predictor variable and average daily step count as the dependent variable. We also studied effect modification by sex by including interaction terms in the regression models. In addition, we performed secondary analyses adjusting our primary model for PAI and waist circumference. We also studied the association of PAI with 10-year CVD risk in model 1 and 2 (similar to our primary analyses).

As we defined a novel threshold of 5 hours of wear time to define a valid day, we adjusted the regression models for wear time and performed sensitivity analyses leveraging an alternate threshold of 10 hours (threshold used in prior accelerometer-based studies).[14,15,22] Similarly, we used a novel threshold of 30 valid days to capture habitual physical activity from the smartwatch and avoid bias related to short-term modification of physical activity. To validate our findings, we also performed sensitivity analyses excluding participants with fewer than 60 or 90 valid days. Significant association was defined by 2-sided $P<0.05$. All statistical analyses were performed using R software package version 3.5.0 (https://www.r-project.org/).

RESULTS

Final study sample included 903 participants (mean age 53±9 years, 61% women, 9% non-White). Most of participants (n=807) were from the Third Generation cohort; the remaining participants were from the New Offspring Spouse cohort (n=13) and the multiethnic Omni 2 cohort (n=83). The median 10-year predicted CVD risk was 2.1% (IQR=4.2%). The predicted CVD risk was higher in men (4.5% [IQR, 6.1%]) than women (1.2% [IQR, 2.2%], $P=1.3\times10^{-26}$). Approximately 9% of participants (n=78) had CVD risk ≥10%; only 6 participants (0.7%) had 10-year risk of CVD ≥30% (Online Figure I).

In Table 1, we present and compare the baseline clinical characteristics of participants with predicted 10-year CVD risk ≥10% to those with predicted risk <10%. As expected, the participants with ≥10% predicted CVD risk were older, more likely to be men, had higher mean BMI and BP, and were more likely to have diabetes mellitus and hypertension. The average self-reported PAI was similar between the participants with ≥10% CVD risk and those with <10% CVD risk. Participants with low CVD risk scores were more likely to be employed compared with those with high CVD risk. There was no significant difference in terms of race, total cholesterol, and smoking status. We also compared the baseline characteristics of participants in this study to those who attended the research center examination and eFHS cohort participants (Online Table I). Overall, eFHS participants were slightly younger (53 versus 55 years old), more likely to be female (56.9% versus 53.8%), and had lower predicted CVD risk (4.2% versus 5.6%), compared with all research center examinees. Baseline characteristics were similar between all eFHS participants (n=1948) and those included in the current study.

On average, participants took 7241 median (IQR, 3261) daily steps during the study period, and only 158 participants (17.5%) took >10000 mean daily steps (Figure 2).[11] Median daily step count was similar among men (7202 steps with IQR 3619) and women (7260 steps with IQR, 3068; $P=0.52$). The most active

Table 1. Characteristics of the Study Participants Stratified by Predicted CVD Risk

Characteristics*	CVD Risk <10% (n=825)	CVD Risk ≥10% (n=78)	*P* Value†
Age, y	52±8	64±6	5.5×10^{-31}
Female sex, n (%)	539 (65.3)	12 (15.4)	5.6×10^{-18}
Body mass index, kg/m^2	28.0±5.6	30.4±4.4	2.3×10^{-6}
Systolic blood pressure, mm Hg	116±13	133±13	8.2×10^{-21}
Diastolic blood pressure, mm Hg	75±8	80±9	2.0×10^{-7}
Total cholesterol, mg/dL	191±35	189±42	0.40
High-density lipoprotein (HDL), mg/dl	63±20	51±16	5.8×10^{-8}
Current smoking, n (%)	38 (4.6)	5 (6.4)	0.41
Diabetes mellitus, n (%)	24 (2.9)	21 (26.9)	2.4×10^{-12}
Hypertension, n (%)	175 (21.2)	52 (66.7)	4.7×10^{-16}
Hypertension treatment, n (%)	138 (16.7)	42 (53.8)	2.3×10^{-12}
Physical activity index	33.2±4.6	34.7±5.8	0.05
Married, living as married, living with partner	625 (75.8)	57 (73.1)	0.58
Self-reported health, excellent	214 (25.9)	14 (17.9)	0.13
Employed full time	591 (71.6)	39 (50.0)	1.5×10^{-4}
Race, self-reported			
White	752 (91.2)	71 (91.0)	1.00
Black	15 (1.8%)	4 (5.1)	0.07
Others	58 (7.0)	3 (3.8)	0.35

CVD indicates cardiovascular disease; and HDL, high-density lipoprotein.

*Presented are mean±SD for continuous traits and n (%) for dichotomous traits.

†*P* value was calculated by Wilcoxon Rank-Sum test for continuous variables and Fisher exact test for categorical variables (without multiple testing correction).

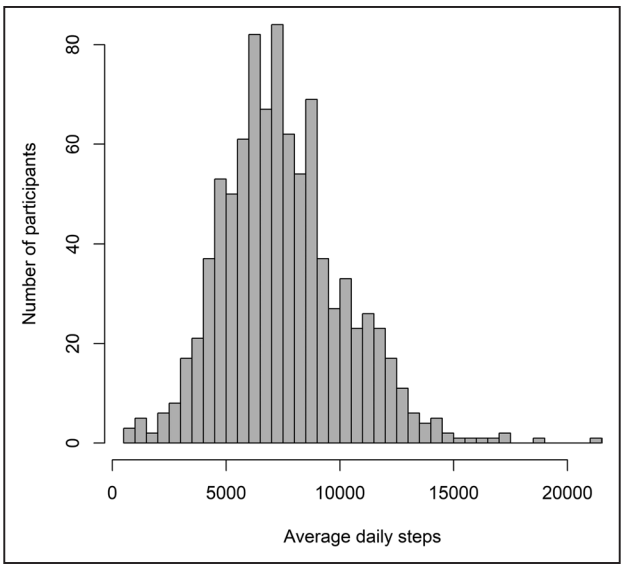

Figure 2. Average daily steps among study participants.
The participants took median of 7241 daily steps.

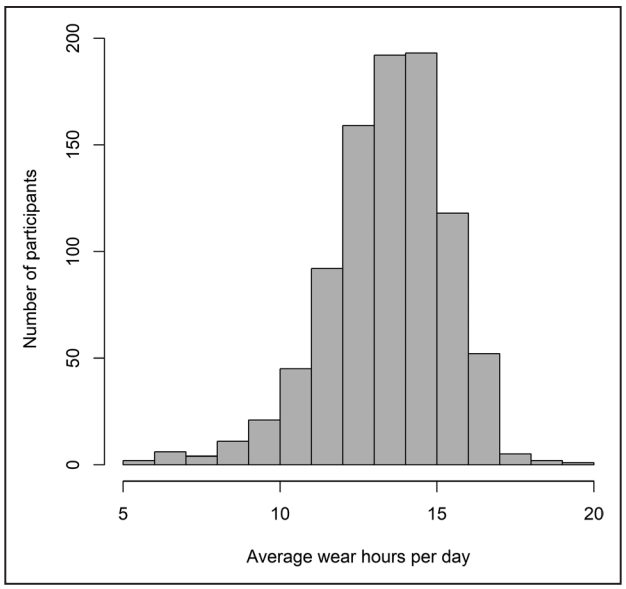

Figure 3. Average daily watch wear time in study participants.
Median wear time was 13.6 h per day.

participant's daily step count was 21 030 averaged over 344 valid days.

Overall, participants were active for a median 13.6 (IQR, 2.4) hours per day (Figure 3), with a median number of valid days at 325 (IQR, 385; Online Figure II). A total of 602 (66.7%) participants had ≥200 valid days and 395 (43.7%) participants had ≥365 valid days during the study period. As expected, participants took most of their steps during daytime hours (6 AM to 6 PM, 67% of steps; Online Figure III). We also compared daily activity during weekdays (Monday to Friday) and weekends (Saturday and Sunday), weekday and weekend daily activity were highly correlated (correlation coefficient=0.80; Online Figure IV). Participants tended to be slightly more active during weekends comparing to weekdays (median 7263 daily steps versus 7168 daily steps), but the difference was not statistically significant (P=0.61). As shown in Online Table II and Online Figure V, only a modest correlation was observed between PAI and daily steps reported from Apple Watch (correlation coefficient=0.29).

We examined the association of physical activity with 10-year predicted CVD risk. In the linear mixed effects model (model 1), daily step count was inversely associated with predicted CVD risk—an increase of 1000 steps per day was associated with 0.18% lower predicted CVD risk (P=3.2×10^{-4}; Table 2), and the effect of each covariate was shown in Online Table III. Results were similar in a sensitivity analysis with CVD risk as the predictor variable and average daily step count as the dependent variable (Online Table IV). In sex-stratified analyses, the strength of association appeared to be slightly stronger in men than in women (0.28% lower 10-year predicted CVD risk in men versus 0.13% lower risk in women per 1000 increase in daily step count). In our model 2, further adjusting model 1 for BMI attenuated the association between step count and predicted CVD risk, which was still statistically significant in sex-pooled analyses (P=0.01) and in men (Table 2). With further adjustment for hypertension, dyslipidemia, and diabetes mellitus in model 3, the association between physical activity and CVD risk attenuated (P=0.05; Online Table V).

In secondary analyses, we first adjusted model 1 for PAI and findings remained largely unchanged (Online Table VI). We also adjusted the regression model for waist circumference. This led to slight attenuation of the association between physical activity and 10-year CVD risk (similar to model 2 in our primary analyses in which we adjusted for BMI). In sensitivity analyses using ≥60 days or ≥90 valid days thresholds, results of model 1 and model 2 were similar (Online Table VII). Furthermore, similar results were obtained using a threshold of 10 hours wear time (instead of 5 hours) to define valid days (Online Table VIII). We also examined the association of PAI with 10-year CVD risk. As shown in Online Table IX, no association was found (P=0.65).

DISCUSSION

In this study, we characterized the patterns of habitual physical activity in a community-based sample of adults using a study smartwatch. Higher levels of daily physical activity were associated with lower predicted risk of CVD, even after adjustment for age, sex, watch wear time, familial structure, and BMI.

There is an abundance of highly congruent data supporting the associations between level of daily physical activity and risk of incident CVD and death.[1–7] Initial evidence was based on self-reported physical activity,[1,2]

Table 2. Association of Average Daily Step Count With 10-y Predicted CVD Risk

	Model 1*			Model 2*		
	β†	SE	*P* Value	β	SE	*P* Value
All participants	−0.18%	0.05%	3.2×10^{-4}	−0.13%	0.05%	0.01
Men	−0.28%	0.09%	0.002	−0.25%	0.10%	0.008
Women	−0.13%	0.05%	0.009	−0.08%	0.05%	0.12

Ten-year CVD risk was estimated using ACC/AHA CVD score. The score includes age, sex, race, total cholesterol, high-density lipoprotein cholesterol, blood pressure, treatment for hypertension, diabetes mellitus, and smoking. ACC indicates American College of Cardiology; AHA, American Heart Association; BMI, body mass index; CVD, cardiovascular disease; and FHS, Framingham Heart Study.

*The model 1 was adjusted for age, sex (for the model including all participants), wear time, and familial structure in FHS. The model 2 was additionally adjusted for BMI.

†β represents the change in 10-y CVD risk for every 1000 increase in daily steps.

but large population-based samples have since leveraged short-term (1 week) deployment of accelerometers to further strengthen the evidence.[14,15] To the best of our knowledge, no prior studies have leveraged activity data collected by a consumer-level wearable activity tracker to study relations between physical activity with predicted risk of CVD. The eFHS was launched with the goal of enriching existing information about FHS participants with mobile and digital health data (including from a smartwatch, home BP monitor, and study smartphone application).[19] Our current investigation represents a key first step toward enhancing understanding of how habitual physical activity relates to the predicted clinical CVD risk. The participants were enrolled during their research center examination, and we did not rely on participants owning the smartwatch, which helped us collect the physical activity data in a comprehensive and systematic manner.

Our observation that patterns of physical activity were related to predicted CVD risk are consistent with prior studies in which physical activity was measured by deploying accelerometers over shorter periods. Notably, in a cohort derived from the Women's Health Initiative, light physical activity was associated with lower risk of incident CVD over average follow-up of ≈3.5 years.[14] Similarly, in select participants of the National Health and Nutrition Examination Survey (2003–2006), all intensities of measured physical activity were associated with risk of all-cause mortality over median follow-up of 6.6 years.[15] Several other studies have reported cross-sectional associations between accelerometer-based measures of physical activity with superior CVD risk prediction.[22,27–29] In a subsample of a Finnish population-based cohort using a wrist-worn accelerometer for 7 days, average daily step count was significantly higher for participants with FHS-CVD predicted risk of <10% (7280 steps/day), compared with those with predicted risk of 10% to 30% (5970 steps/day).[28] Several other population-based studies have reported cross-sectional associations of accelerometer-measured physical activity with markers of cardiometabolic health, including lower levels of insulin resistance.[22,27,29]

Whereas prior studies pointed to a causal relation between physical activity and lower likelihood of incident CVD, short-term use of accelerometers might have led to short-term changes in the behavior of study participants, which may not reflect habitual behaviors, as has been observed previously.[17,18] Furthermore, questionnaires for self-reported physical activity also perform poorly when assessing levels of habitual light physical activity, which constitute the majority of wake active hours.[12,13] Interestingly, in our study, self-reported PAI had only modest correlation with the average daily step count measured using the Apple Watch, and we did not observe any significant association of PAI with 10-year CVD risk. Our findings suggest that the physical activity questionnaires such as PAI are suboptimal for quantifying habitual physical activity. Therefore, digital phenotyping of habitual physical activity using commercial wearable devices designed for longer-term use (such as Apple Watch, Fitbit, etc) provide rich opportunities to study associations between longer-term patterns of physical activity with CVD risk in population-based settings. These devices may also provide a powerful tool delivering, and monitoring the impact, of health interventions focused on activity promotion.

The American College of Cardiology/American Heart Association pooled cohort risk score is the most contemporary CVD prediction model, leveraged widely by clinicians to estimate the risk of CVD and initiate primary prevention therapies such as statins.[24] To date, owing to the paucity of data demonstrating clinical relevance for activity data from activity monitors, clinicians have not systematically incorporated physical activity measures from wearable devices into their estimation of CVD risk. To that end, our study provides important initial evidence that activity patterns as measured from commercially available activity trackers offers important insight into predicted CVD risk. Importantly, 91% of our study participants had 10-year predicted CVD risk <10%, and our findings suggest that the habitual physical activity patterns differ in relation to baseline cardiovascular risk factors (and predicted CVD risk) even in individuals at otherwise intermediate or low risk of CVD. Interestingly, several large healthcare organizations have started to integrate the data from smart devices into their electronic health record systems.[30] If indeed the smartwatch-measured habitual physical activity proves to be a powerful

discriminator for incident CVD risk, the smartwatch data could be integrated into the health records as a vital sign.

Our study has several limitations. First, the majority of participants in our study are White participants with higher level of educational attainment, socioeconomic status, and had higher average daily step count (7241 steps/day) than average US adults (4774 steps/day, measured using a smartphone app).[31] Similar to a representative sample of American smartwatch users, our study sample largely consisted of middle-aged adults (average age 53±9 years) and the role of ambulatory phenotyping using smartwatches in older adults remains largely unexplored. We acknowledge that the 903 participants represented a subset of the 3521 participants attending the index research examination, and they are relatively healthier with lower levels of risk factors and predicted CVD risk. Our findings should be validated in other samples with greater racial and socioeconomic diversity. Second, our analyses were cross-sectional and observational; our study cannot establish causal links between physical activity and incident CVD, and we cannot exclude residual confounding. As the eFHS participants are followed over the next few years, we plan on studying how their patterns of habitual physical activity relate to incident CVD events. Third, whereas we report a statistically significant association between average daily steps and estimated CVD risk, the clinical significance of the magnitude of association we report is uncertain. Fourth, although the algorithm used by the study smartwatch to measure step count has been reported to have high degrees of accuracy for step counts,[32,33] the details of the algorithms used to estimate step count are not available publicly. Therefore, step counts can vary widely by device brand and algorithms or analytical decisions.[34] Fifth, unlike prior accelerometer-based studies, in our current investigation, we did not study various intensities of physical activity (eg, light, moderate, and vigorous) because the accuracy of the study smartwatch in discriminating intensities of physical activity has not been validated.[32,35,36] Sixth, we excluded participants in eFHS enrolled after Jan 31, 2019 who will be contributing to future investigations.

CONCLUSIONS

In this community-based sample of routinely well-phenotyped adults, higher levels of habitual physical activity measured by smartwatch were associated with lower predicted 10-year CVD risk. Future studies should investigate the patterns and level of mobile health-assessed physical activity in relation to incident CVD and the ability of mobile health interventions promoting activity on future CVD risk.

ARTICLE INFORMATION

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Supplemental Materials

Online Supplement
Online Tables I–IX
Online Figures I–V

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