Bidirectional associations of accelerometer measured sedentary behavior and physical activity with knee pain, stiffness, and physical function: The CARDIA study

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ABSTRACT

The objective was to examine bidirectional associations of accelerometer estimated sedentary time and physical activity with reported knee symptoms. Participants were 2,034 adults (mean age 45.3 ± 3.6 years, 58.7% female) from CARDIA. Generalized estimating equations for logistic regression and linear mixed regression models examined associations of accelerometer estimated sedentary time, light-intensity physical activity (LPA), and moderate-to-vigorous intensity physical activity (MVPA) at baseline (2005–06) with knee discomfort, pain, stiffness, and physical function (yes/no and continuous scores from short-form WOMAC function scale) at the 5- and 10-year follow-up exams. Linear regression models examined associations between knee symptoms at the 5-year follow-up with accelerometer estimates at the 10-year follow-up. Models were adjusted for confounders; individuals with comorbidities were excluded in sensitivity analyses. A 30 min/day increment in sedentary time at baseline was associated with lower odds of knee symptoms at the 5- and 10-year follow-up (OR: 0.95, 95% CI range: 0.92–0.98), while LPA and MVPA were associated with greater odds of knee symptoms (LPA OR range: 1.04–1.05, 95% CI range: 1.01–1.09; MVPA OR range: 1.17–1.19, 95% CI range: 1.06–1.32). Report of knee symptoms at the 5-year follow-up was associated with 13.52–17.51 (95% CI range: −29.90, −0.56) fewer minutes/day of sedentary time and 14.58–17.51 (95% CI range: 2.48, 29.38) more minutes/day of LPA at the 10-year follow-up, compared to those reporting no symptoms. Many associations were no longer statistically significant when excluding individuals with comorbidities. Findings support a bidirectional association of accelerometer estimated sedentary time and physical activity with knee symptoms across midlife.

1. Introduction

Osteoarthritis (OA) is one of the leading contributors to global disability (Cross et al., 2014), affecting 13.4% of the U.S. adult population (Cisternas et al., 2016), with the knee being the most common anatomical site (Nguyen et al., 2011; Vos et al., 2012). Given the aging population and high rates of obesity, the prevalence of OA is expected to increase by 50% over the next 20 years, contributing to substantial individual and socioeconomic burden (Hunter et al., 2014). Symptoms of OA include pain, stiffness, and functional limitations, which may be exacerbated by excessive mechanical stress (i.e., obesity), whereas appropriate mechanical stimuli, such as regular physical activity, has

been shown to have a protective effect on joint health among those with OA (Hunter and Eckstein, 2009).

There is strong evidence that greater amounts of physical activity are associated with decreased pain and improved physical function in adults with knee OA (Department of Health and Human Services, 2018; Bartels et al., 2016; Chang et al., 2016; Fransen et al., 2015). Whether a dose–response relationship exists between physical activity and knee symptoms remains unclear (Department of Health and Human Services, 2018). Most research to date on knee pain, stiffness, and physical function has focused on moderate-to-vigorous-intensity physical activity (MVPA), while less is known about the effects of sedentary time or light-intensity physical activity (LPA). This gap in knowledge has important public health implications as some adults may be more willing and able to engage in LPA compared to MVPA. Few studies have examined how knee pain, stiffness, and physical function influence subsequent physical activity, and there is little information on the bidirectional associations of physical activity with knee symptoms. Furthermore, literature investigating knee symptoms has largely been restricted to individuals diagnosed with knee OA, yet half of individuals who complain of knee pain have no radiographic evidence of OA (Hannan et al., 2000). Therefore, it is important to examine the bidirectional associations of sedentary behavior and physical activity with knee symptoms in a population-based sample that is not exclusive to those diagnosed with knee OA. Finally, many of the studies on physical activity and knee symptoms are cross-sectional, and there is a need to examine whether earlier life physical activity is associated with subsequent knee symptoms, and similarly, whether earlier life knee symptoms is associated with subsequent physical activity.

The Coronary Artery Risk Development in Young Adults Study (CARDIA) study provides an opportunity to examine the bidirectional associations between accelerometer-estimated physical activity and symptoms of knee discomfort, pain, stiffness, and physical function in a population-based cohort of middle-aged adults. The objectives of the present study are to examine the associations of: (Cross et al., 2014)
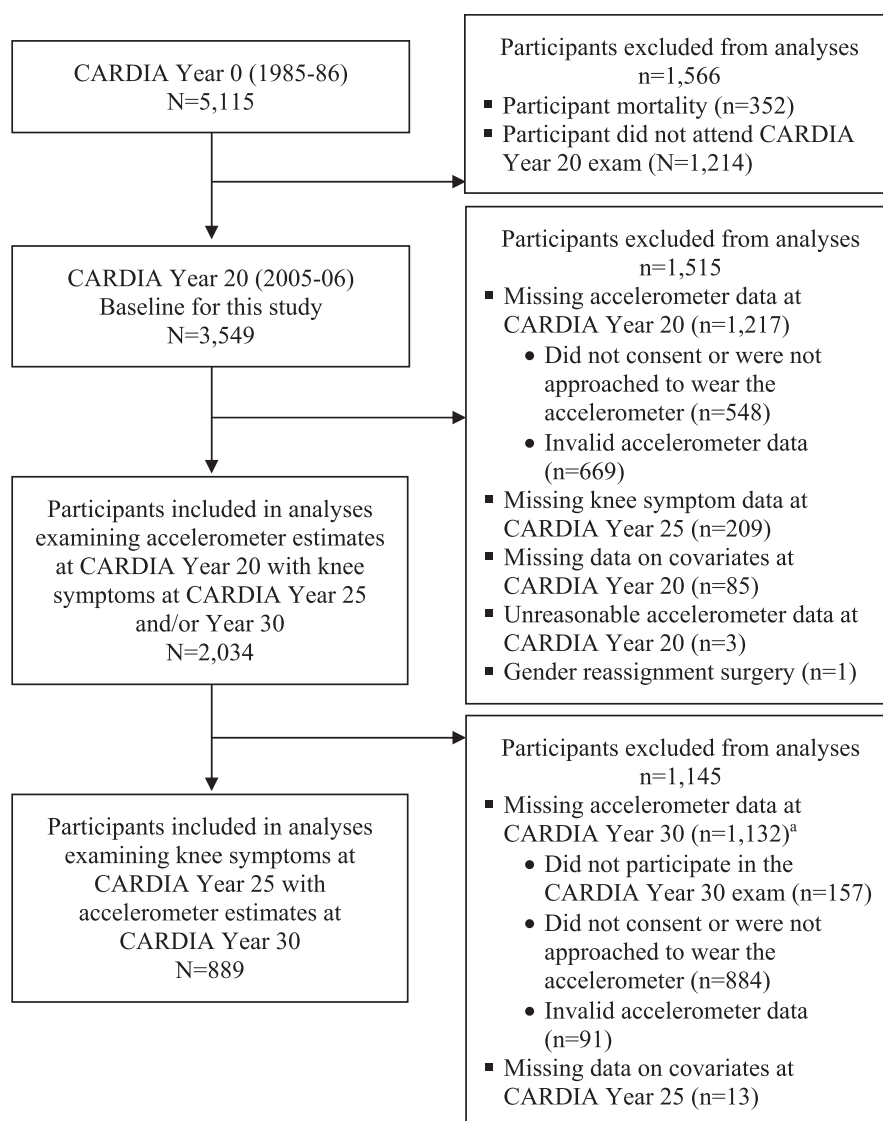
*A total of 3,358 participants took part in the CARDIA Year 30 exam, of which 2,883 were invited to participate in the CARDIA Year 30 Activity Study, which included accelerometer assessment. Of note, the CARDIA Activity Study was funded midway through data collection for the larger CARDIA Year 30 exam, thus resulting in the smaller sample size with accelerometer data compared to Year 20.

Fig. 1. Participant flow diagram for inclusion in analyses, the CARDIA Study (1985–2016).

accelerometer estimated sedentary time, LPA, and MVPA minutes/day assessed in 2005–2006, with participant reported knee symptoms (discomfort, pain, stiffness, and physical function) measured at the 5- and 10-year follow-up, and (Cisternas et al., 2016) knee discomfort, pain, stiffness, and physical function at the 5-year follow-up with accelerometer measured sedentary, LPA, and MVPA at the 10-year follow-up. We hypothesized that sedentary time will be positively and LPA and MVPA inversely associated with knee symptoms, in a dose response and bidirectional relationship. In exploratory analyses we also examined whether the associations differed by race, sex, or body weight status.

2. Methods

2.1. Study participants

CARDIA is an ongoing cohort of 5115 black and white men and women, aged 18–30 years, who took part in an in-person clinical exam in 1985–86 (year 0) at one of four field centers: Birmingham, AL; Minneapolis, MN; Chicago, IL; or Oakland, CA. Additional examinations were held approximately every 2–5 years, including a year 20 (2005–06, ages 38-50 years, baselineforthisanalysis), year 25 (2010–2011, ages 43–55 years, 5–yearfollow–upforthisanalysis) and year 30 (2015–16, ages 48–60 years, 10–yearfollow–upforthisanalysis) exam, with 72%, 72%, and 71% retention of surviving participants, respectively. Details on eligibility criteria, methods of participant selection and follow-up have been previously reported (Friedman et al., 1988). A participant flow diagram detailing inclusion, exclusion, and attrition data can be found in Fig. 1. Briefly, 2034 participants were included in analyses examining associations of accelerometer estimates (independent variables) with knee symptoms assessed at the 5- and 10-year follow-up (dependent variables). Of these participants, 889 were included in analyses examining associations of knee symptoms at the 5-year follow-up (independent variables) with the 10-year follow up accelerometer estimates (dependent variables). Fig. 2 illustrates the timing of the accelerometer and knee symptoms assessments. The institutional review board at each center approved all study protocols. Written informed consent was obtained at each exam, separately for the primary and ancillary studies.

2.2. Accelerometer-based estimates

The ActiGraph 7164 (baseline) and ActiGraph wGT3X-BT (10–yearfollow–up) were initialized to begin data collection at 12:00am on the day of the examination. The monitors were worn at the right hip on an elastic belt during all waking hours for seven days. The 7164 model was initialized to collect data in 60 s epochs, and for the GT3X model, raw triaxial data were sampled at 40 Hz. Data from both devices were processed using ActiLife 6 software, and raw data from the GT3X were reintegrated to a 60 s epoch with the low frequency extension applied to increase sensitivi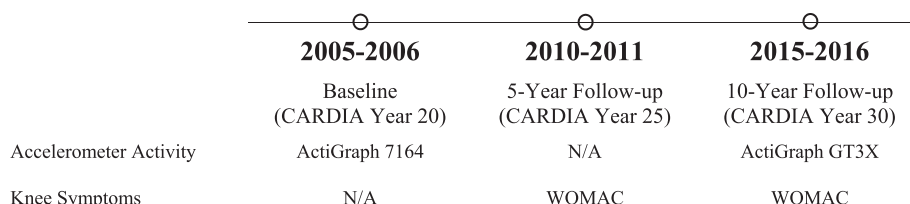ty to low intensity movement (Cain et al., 2013). Files from both devices were screened for wear time using the Troiano algorithm and valid wear time was defined as $\geq$ 4 days of $\geq$ 10 h per day (Troiano et al., 2008); see Supplemental Table 1 for the distribution of valid days at both exams. Minutes spent in different intensity categories using standardized cut-point threshold values. Freedson cut-point threshold values were applied given their broad use in physical activity research, with sedentary time defined as $\leq$ 100 counts per minute (cpm), LPA as 101–1951 cpm, and MVPA as $\geq$ 1952 cpm (Freedson et al., 1998). A calibration factor was applied to the GT3X data to enhance comparability with the 7164 estimates (Whitaker et al., 2018).

2.3. Knee symptoms

At the 5- and 10-year follow-up, participants were asked if they have had any pain or discomfort in their knees in the past month (yes/no, henceforth referred to as knee discomfort). Individuals who responded affirmatively then completed the modified short-form of the Western Ontario and McMaster Universities osteoarthritis index (WOMAC), which includes an assessment of pain (5 items), stiffness (2 items), and physical function (7 items) experienced in the prior two weeks (Yang et al., 2007). The modified short-form of the WOMAC has been demonstrated as a valid, reliable, and responsive alterative to the traditional WOMAC in adults with OA (Yang et al., 2007; Whitehouse et al., 2003) and was found to have adequate responsiveness, content, and construct validity among general practice patients without OA (Heintjes et al., 2008). Response options for each question were none, mild, moderate, severe, or extreme with a corresponding score range from 0 to 4. Possible score ranges for pain, stiffness, physical function, and a composite measure including all three subscales were 0–20, 0–8, 0–28, and 0–56, respectively, with higher scores indicating greater levels of pain, stiffness, and functional limitations. Individuals who responded no to the initial question of having any knee discomfort in the past month did not complete the modified short-form of the WOMAC and were assigned a 0 for each of the subscales. Knee symptoms were analyzed categorically for knee discomfort, pain, stiffness, and function (yes for mild to extreme symptoms vs. no symptoms), as well as continuously (pain, stiffness, function, and the composite measure).

2.4. Covariates

Study covariates from the baseline examination included center and self-reported age, sex, race, and years of education. Body mass index (BMI) was calculated using measured height and weight (kg/m^2). Depressive symptoms were assessed using the 20-items Center for Epidemiologic Studies Depression Scale, and modeled as a dichotomous variable, with scores equal to 16 or higher indicating clinically significant depressive symptoms (Radloff, 1977). Physical quality of life was assessed using the physical component score from the Medical Outcomes Study Short Form (SF-12) (Ware et al., 1996). Comorbidities previously found to be associated with knee OA symptoms and severity (Caporali

	2005-2006	2010-2011	2015-2016
	Baseline (CARDIA Year 20)	5-Year Follow-up (CARDIA Year 25)	10-Year Follow-up (CARDIA Year 30)
Accelerometer Activity	ActiGraph 7164	N/A	ActiGraph GT3X
Knee Symptoms	N/A	WOMAC	WOMAC

Abbreviations: CARDIA = Coronary Artery Risk Development in Young Adults, WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index

Fig. 2. Timeline of accelerometer activity and knee symptoms assessment, the CARDIA Study (2005–2016).

et al., 2005; Nuesch et al., 2011; Peters et al., 2005; Ettinger et al., 1994) included self-reported cardiovascular disease, diabetes, cancer, and respiratory diseases, modeled as yes/no for presence of any comorbidity. Participants were also asked if they had any medical problem(s) that interfered with their ability to exercise over the previous twelve months (yes/no).

2.5. Statistical analyses

Descriptive statistics at baseline were calculated, stratified by baseline tertiles of accelerometer-based MVPA minutes/day, standardized to total wear time. Descriptive statistics at baseline were also stratified by self-reported knee discomfort status (yes/no) at the 5- and 10-year follow-up.

If participants reported experiencing knee discomfort in the past month, the modified short-form of the WOMAC was used to evaluate the presence and extent of knee pain, stiffness, and functional limitations, as well as a composite measure. Generalized estimating equations for logistic regression examined the associations of baseline accelerometer-estimates (sedentary, LPA, and MVPA; independent variables, assessed separately) with the presence of knee discomfort, pain, stiffness, or functional limitations, (yes/no; dependent variables, assessed separately), at the 5- and 10-year follow-up. Among those reporting any knee discomfort, linear mixed model regression was used to examine the associations of baseline accelerometer-estimates with the extent of knee pain, stiffness, functional limitations, and the composite score using the continuous WOMAC scores in separate models. Data on knee symptoms from the 5- and/or 10-year follow-up were used, thereby including in the analyses all participants who had knee symptom data at either exam to preserve a larger sample size with mixed model procedures and provide enhanced precision in our estimates. Before entry into the models, all accelerometer-estimated intensity categories were divided by 30, such that a unit increase in the activity represented an increase of 30 min/day. All models were adjusted for baseline center, race, sex, physical quality of life, and total accelerometer wear time, as well as time varying age, education, BMI, depressive symptoms, and self-reported comorbidities. Data on knee measures were not collected at baseline, so we adjusted for physical quality of life to account for possible differences in physical abilities at baseline. In sensitivity analyses we excluded individuals who responded yes to the question "Do you have any medical problem(s) that interfered with your ability to exercise over the past twelve months?" (N = 336), as an additional method to account for potential differences in knee symptoms at baseline. However, study findings were unchanged, and further analysis revealed no differences between accelerometer-estimated and self-reported physical activity among those who did and did not report medical problems that interfered with ability to exercise (data not shown). In separate sensitivity analyses, we also exclude individuals with the aforementioned comorbidities, rather than adjusting for comorbidities, to better estimate the true association of physical activity on knee symptoms, independent of other health conditions (N = 528). We also examined associations of physical activity and knee symptoms cross-sectionally at the 10-year follow-up exam.

To explore the bidirectional associations of physical activity and knee symptoms, we used linear regression to examine in separate models the associations of knee symptoms at the 5-year follow-up (independent variables) with accelerometer-estimates at the 10-year follow-up (dependent variables). The presence of any knee discomfort, pain, stiffness, and functional limitations (yes/no), as well as extent of knee pain, stiffness, functional limitations, and the composite score (continuous WOMAC scores) were examined in relation to the physical activity estimates. All models adjusted for center, age, sex, race, years of education, BMI, depressive symptoms, comorbidities, and self-reported MVPA from the 5-year follow-up. In sensitivity analyses, we adjusted for accelerometer-estimated MVPA at baseline, rather than self-reported MVPA at the 5-year follow-up. In additional sensitivity analyses, we

excluded individuals with self-reported comorbidities at the 5-year follow-up.

All assumptions of linear regression were verified. As MVPA estimates were skewed, we ran all models using log transformed MVPA; findings were consistent with raw values, therefore for ease of interpretation we present the non-transformed data. Interaction terms were used to examine whether the associations between physical activity and knee outcomes differed by race, sex, or BMI category (BMI < 30 kg/m^2 vs. BMI ≥ 30 kg/m^2).

3. Results

Descriptive information of participants included and excluded from the current study can be found in Supplemental Table 2. Descriptive information among those who were included in analyses examining associations of accelerometer-estimates (baseline) with knee symptoms (5–and10–yearfollow–up) only, compared to those who were included in the aforementioned analyses in addition to the analyses examining knee symptoms (5–yearfollow–up) with accelerometer-estimates (10–yearfollow–up) can be found in Supplemental Table 3. Participant characteristics, stratified by accelerometer-estimated MVPA tertiles are shown in Table 1. MVPA level at baseline was not significantly associated with knee symptoms at the 5-year follow-up exam. However, MVPA level at baseline was associated with knee symptoms at the 10-year follow-up exam, with those who were more active reporting less discomfort, pain, stiffness, functional limitations, and a lower composite knee symptoms score compared to the least active group (all p < 0.05). As seen in Table 2, participants who reported any knee discomfort at the 5-year follow-up (N = 612, 30.1%) or 10-year follow-up (N = 723, 38.6%) were more likely to be older, female, have a greater BMI, more depressive symptoms, reduced physical quality of life, were more likely to report problems that interfered with their ability to exercise, and had more comorbidities.

3.1. Associations of accelerometer estimates with subsequent knee measures

As seen in Table 3, a 30 min/day increment in sedentary time at baseline was associated with lower odds of knee discomfort, pain, stiffness, and functional limitations at both the 5- and 10-year follow-up (OR: 0.95, 95% CI range: 0.92–0.98). A 30 min/day increment in LPA or MVPA was associated with greater odds of knee discomfort, greater pain, stiffness, and functional limitations at follow-up, in a dose response manner (LPA OR range: 1.04–1.05, 95% CI range: 1.01–1.09); MVPA OR range: 1.17–1.19, 95% CI range: 1.06–1.32). In sensitivity analyses, associations of sedentary time and LPA with knee symptoms were largely attenuated when excluding those with comorbidities (Supplemental Table 4). Cross-sectional analyses were largely consistent with our primary longitudinal analyses; however, associations of MVPA with knee symptoms were no longer statistically significant, although effect estimates were in the same direction and similar in magnitude (Supplemental Table 5).

Table 4 shows that among those reporting any knee discomfort, a 30 min/day increment in sedentary time was associated with statistically significant lower WOMAC scores for pain (-0.08 ± 0.03), functional limitations (-0.10 ± 0.05), and the composite score (-0.22 ± 0.08) at follow-up, while a 30 min/day increment in LPA was associated with statistically significant higher scores for pain (0.09 ± 0.04), functional limitations (0.12 ± 0.05), and the composite score (0.23 ± 0.09; all p < 0.05). In sensitivity analyses, associations were no longer significant excluding individuals with comorbidities (Supplemental Table 6). In cross-sectional analyses at the 10-year follow-up, findings between accelerometer estimates and WOMAC scores were similar to those from longitudinal analyses (Supplemental Table 7).

Table 1

Participant Characteristics, Stratified by Moderate-to-Vigorous Intensity Physical Activity (MVPA) Tertile, the CARDIA Study (2005–2016).

Participant characteristics (Baseline)	MVPA Tertile (Baseline)[a]			P-value[b]
	Low N = 678	Medium N = 678	High N = 678	
Age, mean years ± SD	45.2 ± 3.7	45.5 ± 3.6	45.2 ± 3.4	0.255
Female, N(%)	500 (73.8)	379 (55.9)	314 (46.3)	**<0.001**
White, N(%)	317 (46.8)	424 (62.5)	472 (69.6)	**<0.001**
Education, mean years ± SD	14.9 ± 2.5	15.3 ± 2.5	15.6 ± 2.6	**<0.001**
BMI, mean kg/m² ± SD	30.4 ± 7.4	29.0 ± 6.4	27.4 ± 6.8	**<0.001**
High depressive symptoms, N(%)	110 (16.2)	103 (15.2)	92 (13.6)	0.386
Physical quality of life, mean score ± SD	50.39 ± 7.8	52.0 ± 7.1	53.4 ± 5.6	**<0.001**
Medical problems that interfere with ability to exercise, N(%)	109 (16.2)	106 (15.7)	121 (17.9)	0.507
Comorbidities, N(%)[c]	210 (31.0)	172 (25.4)	146 (21.5)	**<0.001**
Cardiovascular disease, N(%)	23 (3.4)	14 (2.1)	13 (1.9)	0.155
Type 2 Diabetes, N(%)	69 (10.3)	50 (7.4)	20 (3.0)	**<0.001**
Cancer, N(%)	36 (5.3)	34 (5.0)	34 (5.0)	0.966
Respiratory disease, N(%)	119 (17.6)	96 (14.2)	94 (13.9)	0.110
Accelerometer estimates				
Total wear time, mean min/day ± SD	876.7 ± 89.1	889.4 ± 86.7	891.8 ± 85.0	**0.003**
Sedentary time, mean min/day ± SD	518.8 ± 99.2	494.3 ± 98.3	452.5 ± 101.1	**<0.001**
LPA, mean min/day ± SD	344.5 ± 86.5	364.8 ± 79.9	376.6 ± 87.4	**<0.001**
MVPA, median min/day ± IQR	13.4 ± 5.3	30.3 ± 6.2	62.7 ± 26.3	**<0.001**
Knee Symptoms (5-year follow-up)				
Discomfort, N(%)	220 (32.5)	182 (26.8)	210 (31.0)	0.066
Modified Short Form WOMAC[d]				
Pain, N(%)	202 (29.8)	164 (24.2)	188 (27.7)	0.064
Pain, mean score ± SD	1.72 ± 3.27	1.39 ± 2.98	1.38 ± 2.72	0.073
Stiffness, N(%)	164 (24.2)	137 (20.2)	129 (19.0)	0.051
Stiffness, mean score ± SD	1.01 ± 1.78	0.82 ± 1.65	0.75 ± 1.39	0.065
Physical function, N(%)	184 (27.1)	147 (21.7)	159 (23.5)	0.057
Physical function, mean score ± SD	2.11 ± 4.35	1.68 ± 3.86	1.43 ± 3.12	0.067
Composite, mean score ± SD	4.84 ± 8.99	3.89 ± 8.19	3.57 ± 6.82	**0.065**
Knee Symptoms (10-year follow-up)	**N = 624**	**N = 633**	**N = 617**	
Discomfort, N(%)	264 (42.3)	222 (35.1)	237 (38.4)	**0.031**
Modified Short Form WOMAC[d]				
Pain, N(%)	251 (40.2)	206 (32.5)	210 (34.0)	**0.010**
Pain, mean score ± SD	2.54 ± 3.86	1.92 ± 3.48	1.63 ± 2.79	**0.002**
Stiffness, N(%)	216 (34.6)	165 (26.1)	185 (30.0)	**0.004**
Stiffness, mean score ± SD	1.41 ± 2.02	1.09 ± 1.80	1.14 ± 1.75	**0.014**
Physical function, N(%)	230 (36.9)	176 (27.8)	178 (28.9)	**<0.001**
Physical function, mean score ± SD	3.00 ± 4.98	2.30 ± 4.49	1.95 ± 3.86	**0.004**
Composite, mean score ± SD	6.95 ± 10.51	5.31 ± 9.43	4.72 ± 7.98	**0.031**

Abbreviations: BMI = body mass index, LPA = light-intensity physical activity, MVPA = moderate-to-vigorous intensity physical activity. Bolded values are statistically significant (p < 0.05).

[a] MVPA minutes/day standardized for total wear time.

[b] P-values testing for differences across physical activity groups using one-way ANOVA, Kruskal Wallis, or Chi-Square tests, as appropriate.

[c] Comorbidities include self-reported cardiovascular disease (myocardial infarction, angina, peripheral vascular disease, stroke or transient ischemic attack), type 2 diabetes, cancer, and respiratory disease (asthma, chronic obstructive pulmonary disease, chronic bronchitis or emphysema).

[d] Individuals who reported no knee discomfort and thus did not complete the Modified Short Form WOMAC were given scores of 0 on the subscales. Possible score ranges for knee pain, stiffness, functional limitations, and the composite score (knee pain + stiffness + functional limitations) ranged from 0 to 20, 0–8, 0–28, and 0–56, respectively, with higher scores indicating more severe pain, stiffness, or functional limitations.

3.2. Associations of knee measures with subsequent accelerometer estimates

As shown in Table 5, individuals reporting knee discomfort, pain, stiffness, or functional limitations at the 5-year follow-up had 13.52–17.61 (95% CI range: −26.48, −0.56) fewer minutes/day of sedentary time and 14.58–17.51 (95% CI range: 2.48, 29.38) more minutes/day of LPA at the 10-year follow-up, compared to those reporting no knee problems (all p < 0.05). There were no associations between knee symptoms and subsequent MVPA. These findings were largely consistent after excluding individuals who reported comorbidities at the 5-year follow-up, although the associations between knee stiffness/ physical function and sedentary time were no longer statistically significant (Supplemental Table 8).

Table 6 shows that a one unit increase in the pain and physical function subscales of the WOMAC at the 5-year follow-up was associated with 0.48 (95% CI: −0.95, −0.01) and 0.44 (95% CI: −0.80, −0.09)

fewer minutes/day of MVPA at the 10-year follow-up, respectively. Findings were consistent when examining the knee outcome measures when adjusting for self-reported physical activity at the 5-year follow-up or accelerometer estimated activity at baseline (data not shown). However, associations were attenuated when excluding individuals who self-reported comorbidities at the 5-year follow-up (Supplemental Table 9).

No interactions were observed for sex, race, or BMI categories across models (all p > 0.05).

4. Discussion

In this population-based cohort of black and white middle-aged adults, we found that higher levels of accelerometer estimated sedentary time was associated with lower odds of self-reported knee symptoms, while higher levels of LPA and MVPA were associated with greater odds of knee symptoms, assessed up to 10 years later. Report of knee

Table 2
Participant characteristics, stratified by self-reported knee discomfort status[a], the CARDIA study (2005–2016).

Participant Characteristics	Knee Discomfort		P-value[b]	Knee Discomfort		P-value[b]
Baseline	5-year follow-up			10-year follow-up		
	Yes	No		Yes	No	
	N = 612	N = 1422		N = 723	N = 1151	
Age, mean years ± SD	45.5 ± 3.4	45.2 ± 3.6	**0.035**	45.5 ± 3.4	45.2 ± 3.6	0.067
Female, N(%)	399 (65.2)	794 (55.8)	**<0.001**	470 (65.0)	633 (55.0)	**<0.001**
White, N(%)	357 (58.3)	856 (60.2)	0.432	427 (59.1)	699 (60.7)	0.493
Education, mean years ± SD	15.1 ± 2.6	15.3 ± 2.5	0.12	15.2 ± 2.5	15.4 ± 2.5	0.125
BMI, mean kg/m^2 ± SD	30.4 ± 8.3	28.3 ± 6.2	**<0.001**	30.3 ± 8.1	28.0 ± 6.0	**<0.001**
High depressive symptoms, N(%)	117 (19.1)	188 (13.2)	**<0.001**	122 (16.9)	158 (13.7)	0.063
Physical quality of life, mean score ± SD	50.1 ± 8.2	52.8 ± 6.2	**<0.001**	50.3 ± 7.9	53.0 ± 6.1	**<0.001**
Medical problems that interfere with ability to exercise, N(%)	142 (23.2)	194 (13.7)	**<0.001**	171 (23.8)	138 (12.0)	**<0.001**
Comorbidities, N(%)[c]	179 (29.3)	349 (24.5)	**0.026**	211 (29.2)	280 (24.3)	**0.02**
Cardiovascular disease, N(%)	19 (3.1)	31 (2.2)	0.217	25 (3.5)	19 (1.7)	**0.012**
Type 2 Diabetes, N(%)	51 (8.4)	88 (6.2)	0.077	58 (8.1)	72 (6.3)	0.134
Cancer, N(%)	29 (4.8)	75 (5.3)	0.616	29 (4.0)	65 (5.7)	0.112
Respiratory disease, N(%)	115 (18.8)	194 (13.6)	**0.003**	137 (19.0)	152 (13.2)	**<0.001**
Accelerometer Estimates (baseline)						
Total wear time, mean min/day ± SD	886.5 ± 85.1	885.7 ± 88.1	0.326	889.3 ± 87.4	885.6 ± 86.5	0.365
Sedentary time, mean min/day ± SD	481.9 ± 104.2	491.4 ± 102.6	0.057	485.6 ± 105.2	492.8 ± 101.2	0.143
LPA, mean min/day ± SD	369.0 ± 86.4	359. ± 85.2	**0.016**	368.3 ± 86.4	357.4 ± 84.5	**0.007**
MVPA, median min/day ± IQR	29.1 ± 31.4	29.8 ± 28.4	0.827	28.9 ± 30.4	30.1 ± 28.4	0.178
Accelerometer Estimates (10-year follow-up)	**N = 298**	**N = 604**		**N = 352**	**N = 549**	
Total wear time, mean min/day ± SD	894.7 ± 89.2	892.8 ± 86.3	0.754	891.8 ± 882.8	894.4 ± 887.0	0.663
Sedentary time, mean min/day ± SD	523.2 ± 103.3	536.4 ± 101.9	0.069	525.7 ± 515.3	536.2 ± 527.4	0.133
LPA, mean min/day ± SD	343.7 ± 333.8	326.8 ± 82.9	**0.005**	338.8 ± 90.4	328.2 ± 80.2	0.075
MVPA, median min/day ± IQR	21.7 ± 31.4	24.3 ± 28.2	0.122	22.6 ± 28.1	24.2 ± 30.2	0.152

Abbreviations: BMI = body mass index, LPA = light-intensity physical activity, MVPA = moderate-to-vigorous intensity physical activity. Bolded values are statistically significant (p < 0.05).
[a]Self-reported knee discomfort assessed by asking if participants had any pain or discomfort in the knees in the past month.
[b]P-values assessing differences in participant characteristics at baseline by knee discomfort status, assessed at the 5- and 10-year follow-up, using independent samples t-tests, Wilcoxon-Mann Whitney tests, or chi-square tests, as appropriate.
[c]Comorbidities include self-reported cardiovascular disease (myocardial infarction, angina, peripheral vascular disease, stroke, transient ischemic attack), type 2 diabetes, cancer, and respiratory disease (asthma, chronic obstructive pulmonary disease, chronic bronchitis, emphysema).

Table 3
Generalized estimating equations for logistic regression analyses examining accelerometer estimates at baseline with the presence of self-reported knee discomfort, pain, stiffness, and functional limitations (yes/no) at the 5- and 10-year follow-up, the CARDIA Study, N = 2034 (2005–2016).

Accelerometer Estimates[a]	Knee Measures (Yes/No)											
	Discomfort			Pain			Stiffness			Physical Function		
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
Sedentary	0.95	0.92, 0.98	**<0.001**	0.95	0.93, 0.98	**0.002**	0.95	0.92, 0.98	**0.001**	0.95	0.92, 0.98	**0.002**
LPA	1.04	1.01, 1.08	**0.007**	1.04	1.01, 1.08	**0.013**	1.05	1.01, 1.09	**0.007**	1.04	1.01, 1.08	**0.013**
MVPA	1.18	1.07, 1.29	**<0.001**	1.17	1.07, 1.29	**0.001**	1.19	1.08, 1.32	**0.001**	1.17	1.06, 1.29	**0.002**

Abbreviations: LPA = light-intensity physical activity; MVPA = moderate-to-vigorous intensity physical activity.
Models adjusted for baseline center, race, sex, physical quality of life, and total accelerometer wear time, and time varying age, education, body mass index, depressive symptoms, and comorbidities (cardiovascular disease, type 2 diabetes, cancer, respiratory disease). Odds ratios are interpreted per 30 min/day increment in the accelerometer estimates. Bolded values are statistically significant (p < 0.05).
[a] Sedentary time defined as 0–100 counts per minute; LPA as 101–1951 counts per minute; MVPA as ≥ 1952 counts per minute.

Table 4
Linear mixed model regression analyses examining accelerometer estimates at baseline with the extent of self-reported knee pain, stiffness, and functional limitations (continuous WOMAC scores) among those who reported any knee discomfort at the 5- and 10-year follow-up, the CARDIA Study, N = 1310, (2005–2016).

Accelerometer Estimates[a]	Knee Measures (WOMAC Scores)											
	Pain			Stiffness			Physical Function			Composite		
	Beta	SE	p-value	Beta	SE	p-value	Beta	SE	p-value	Beta	SE	p-value
Sedentary	−0.08	0.03	**0.014**	−0.03	0.02	0.072	−0.10	0.05	**0.024**	−0.22	0.08	**0.010**
LPA	0.09	0.04	**0.015**	0.03	0.02	0.158	0.12	0.05	**0.018**	0.23	0.09	**0.012**
MVPA	0.08	0.11	0.449	0.09	0.05	0.091	0.05	0.15	0.741	0.23	0.28	0.414

Abbreviations: LPA = light-intensity physical activity; MVPA = moderate-to-vigorous intensity physical activity.
Models adjusted for baseline center, race, sex, physical quality of life, and total accelerometer wear time, and time varying age, education, body mass index, depressive symptoms, and comorbidities (cardiovascular disease, type 2 diabetes, cancer, respiratory disease). Beta coefficients are interpreted per 30 min/day increment in the accelerometer estimates. Bolded values are statistically significant (p < 0.05).
[a] Sedentary time defined as 0–100 counts per minute; LPA as 101–1951 counts per minute; MVPA as ≥ 1952 counts per minute.

Table 5
Linear regression analyses examining associations of self-reported knee discomfort, pain, stiffness, and functional limitations (yes/no) at the 5-year follow-up with accelerometer estimates at the 10-year follow-up, the CARDIA study, N = 889 (2010–2016).

Knee Measures (Yes/No)	Accelerometer Estimates[a]								
	Sedentary			LPA			MVPA		
	Beta	95% CI	p-value	Beta	95% CI	p-value	Beta	95% CI	p-value
Discomfort	−16.39	−28.29, −4.49	**0.007**	15.81	4.69, 26.92	**0.005**	0.58	−2.42, 3.59	0.703
Pain	−17.61	−29.90, −5.32	**0.005**	17.51	6.04, 28.99	**0.003**	0.10	−3.01, 3.20	0.952
Stiffness	−14.90	−28.64, −1.15	**0.034**	16.54	3.71, 29.38	**0.012**	−1.65	−5.12, 1.82	0.351
Physical Function	−13.52	−26.48, −0.56	**0.041**	14.58	2.48, 26.68	**0.018**	−1.05	−4.32, 2.21	0.526

Abbreviations: LPA = light-intensity physical activity; MVPA = moderate-to-vigorous intensity physical activity.
Models adjusted for 5-year follow-up center, race, sex, age, education, body mass index, depressive symptoms, comorbidities (cardiovascular disease, type 2 diabetes, cancer, respiratory disease), self-reported MVPA and 10-year follow-up total accelerometer wear time. Bolded values are statistically significant (p < 0.05).
[a] Sedentary time defined as 0–100 counts per minute; LPA as 101–1951 counts per minute; MVPA as ≥ 1952 counts per minute.

Table 6
Linear regression analyses examining associations of self-reported knee pain, stiffness, and functional limitations (continuous WOMAC scores) at the 5-year follow-up with accelerometer estimates at the 10-year follow-up, the CARDIA study, N = 889 (2010–2016).

Knee Measures (WOMAC Scores)	Accelerometer Estimates[a]								
	Sedentary			LPA			MVPA		
	Beta	95% CI	p-value	Beta	95% CI	p-value	Beta	95% CI	p-value
Pain	−0.45	−2.32, 1.42	0.635	0.93	−0.81, 2.68	0.294	−0.48	−0.95, −0.01	**0.044**
Stiffness	−1.92	−5.15, 1.31	0.243	2.31	−0.70, 5.33	0.133	−0.39	−1.20, 0.42	0.342
Physical Function	−0.35	−1.78, 1.07	0.627	0.80	−0.54, 2.13	0.241	−0.44	−0.80, −0.09	**0.015**
Composite	−0.37	−1.12, 0.39	0.340	0.51	−0.19, 1.21	0.155	−0.14	−0.33, 0.05	0.137

Abbreviations: LPA = light-intensity physical activity; MVPA = moderate-to-vigorous intensity physical activity.
Models adjusted for 5-year follow-up center, race, sex, age, education, body mass index, depressive symptoms, comorbidities (cardiovascular disease, type 2 diabetes, cancer, respiratory disease), self-reported MVPA and 10-year follow-up total accelerometer wear time. Bolded values are statistically significant (p < 0.05).
[a] Sedentary time defined as 0–100 counts per minute; LPA as 101–1951 counts per minute; MVPA as ≥ 1952 counts per minute.

symptoms were also associated with less sedentary time and more LPA five years later. Bidirectional study findings were less robust when examining the extent of knee symptoms among those reporting any knee discomfort, as determined by the short form of the WOMAC. Further, bidirectional associations were largely attenuated when excluding individuals with comorbidities known to be associated with knee symptom severity.

While our findings did not support our original hypothesis, results are in line with those from Liu and colleagues, who observed that higher levels of accelerometer estimated LPA and MVPA were associated with worsening physical function (LPA only) and increased pain (LPA and MVPA) assessed by the WOMAC over 1-year among participants in the Osteoarthritis Initiative with radiographically confirmed knee OA (Liu et al., 2016). It is possible that the cause of knee discomfort in the present study was not due to underlying knee OA, but other conditions, such as patellofemoral pain, which may in part explain our unanticipated findings given that greater physical activity levels may overload the knee joint, which can elicit or exacerbate conditions such as patellofemoral pain (Petersen et al., 2014).

Interestingly, the associations of accelerometer estimates with reported knee symptoms observed in the present study were largely attenuated when excluding individuals with comorbidities, with the exception that baseline MVPA remained associated with knee symptoms at follow-up. One potential interpretation of this finding is that individuals without comorbidities do not perceive sedentary time and LPA to contribute to knee symptoms, while individuals with comorbidities perceive these lower intensity behaviors to have a greater impact on knee pain, stiffness, and functional limitations. There is limited understanding of how comorbid health conditions affect individuals' perceptions of OA symptoms. However, Zullig and colleagues reported that among U.S. Veterans with hip and knee OA, comorbid conditions were associated with worse scores on patient related outcomes, including pain and physical function measures (Zullig et al., 2015). Given the high

prevalence of comorbidities experienced by individuals reporting knee symptoms (~30% in the present study), there is a need for additional research to examine how other health conditions influence the relation of physical activity patterns with knee symptoms. It is also possible that individuals with comorbidities may have already altered their activity patterns prior to baseline due to their health conditions, or were more likely to have knee symptoms at baseline than those without comorbidities, which could potentially strengthen associations between activity and knee symptoms in this population.

We also found that individuals reporting any knee symptoms had less sedentary time and more LPA five years later. Given the growing evidence from randomized controlled trials of the benefits of physical activity for reducing OA symptoms and severity (Department of Health and Human Services, 2018; Fransen et al., 2015), it is possible that knee symptoms led individuals to make positive changes to their physical activity patterns by incorporating more LPA. This increase in LPA is in line with current guidelines that specify regular physical activity as a core non-surgical recommendation for knee OA management (McAlindon et al., 2014). Alternately, it is possible that knee symptoms lead to more discomfort while seated for prolonged time, thus encouraging movement in the form of LPA. However, higher WOMAC scores for pain, stiffness, and physical function were associated with less MVPA five years later. This is compatible with findings from Song et al., who observed that greater levels of knee pain were associated with fewer minutes/day of accelerometer estimated MVPA, but not LPA, among participants in the Osteoarthritis Initiative (Song et al., 2018). Taken together, these findings provide support that among those with knee symptoms, LPA may be a more feasible and acceptable means of activity compared to MVPA.

Notably, we observed that the bi-directional associations of accelerometer estimates with the extent of knee stiffness were less robust compared to findings for knee pain or physical function. However, this may be due to the smaller sample who reported knee stiffness compared

to the other outcomes.

Major strengths of this study include accelerometer assessment of sedentary behavior and physical activity, which is less prone to bias (Sallis and Saelens, 2000), multiple accelerometer measures which allowed for the exploration of the bidirectional associations with knee symptoms, use of a population-based sample, and ability to look at differences by race, sex, and BMI category. However, there are several study limitations. First, we did not assess knee symptoms at baseline, and therefore weren't able to assess change in symptoms across time. However, we attempted to control for baseline differences in knee symptoms by adjusting for physical quality of life and in sensitivity analyses excluding individuals who reported any medical problems that interfered with their ability to exercise. In addition, we examined associations between accelerometer estimates and knee symptoms cross-sectionally at the 10-year follow-up and our findings were largely consistent with longitudinal analyses, thus providing additional support for our primary findings. We did not have accelerometer measures at the year 25 exam; however, we attempted to control for differences in physical activity by adjusting for self-reported activity at this exam, and in sensitivity analyses we alternately adjusted for baseline accelerometer activity as a proxy for the 5-year follow-up activity. Despite these considerations, the potential for reverse causality remains. The waist-worn accelerometers can misclassify standing time (LPA) as sedentary time which may have implications for the observed associations with knee symptoms (Kerr et al., 2013). CARDIA also does not include imaging data to confirm the presence of knee OA; however, many individuals with radiographically confirmed knee OA do not report symptoms (Hannan et al., 2000), and self-reported symptoms are arguably more important for quality of life. It is also plausible that knee symptoms were not due to knee OA, but rather other unmeasured underlying conditions. While we adjusted for many potential confounders, residual confounding is a possibility and results should be interpreted with caution. For example, we did not have a detailed assessment on the physical activity context, such as occupational vs. leisure activity, or information on prior history of knee injury. Finally, the sample included in these analyses were generally healthier than those excluded, thus limiting generalizability to the larger CARDIA cohort and general population.

5. Conclusion

Our hypothesis that sedentary time would be positively and LPA and MVPA inversely associated with the presence and severity of participant reported knee symptoms was not supported. Interesting, observed associations were largely attenuated when excluding individuals with comorbidities, indicating that overall health status may be related to one's perception of knee symptoms as it relates to physical activity patterns. Future research is needed to further explore the role of comorbidities when studying physical activity and knee symptoms.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pmedr.2021.101348.

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