

TITLE PAGE

Full title of manuscript (maximum of 20 words):

A Decline in Walking Speed is Associated with Incident Knee Replacement in Adults with and at Risk for Knee Osteoarthritis

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Short running head (maximum of 4 words):

Walking Speed and KR

ABSTRACT

Objective: To determine if a one-year change in walking speed is associated with receiving an incident knee replacement during the following year in adults with and at risk for knee osteoarthritis (OA).

Methods: Using data from the Osteoarthritis Initiative, we determined a one-year change in 20-meter walk speed from three observation periods (i.e., 0-12, 12-24, and 24-36 month). We operationally defined one-year change in walking speed as either: 1) decline: < -0.1 m/s change, 2) no change: between -0.1 and 0.1 m/s change, 3) increase: > 0.1 m/s change. Incident knee replacement was defined using each subsequent one-year period (i.e., 12-24, 24-36, and 36-48 month). Combining data from the three observation periods, we performed a Poisson regression with robust error variance to determine the relative risk between a change in walking speed (exposure) and incident knee replacement over the following year (outcome).

Results: Of the 4,264 participants included within this analysis (11,311 total person visits), 115 (3%) adults received a knee replacement. Decline in walking speed was associated with a 104% increase in risk [adjusted relative risk (RR)=2.04; 95% confidence interval (CI)= 1.40-2.98], while an increase in walking speed associated with a 55% decrease in risk (RR=0.45; 95% CI=0.22-0.93) of incident knee replacement in the following year compared to a person with no change in walking speed.

Conclusions: A one-year decline in walking speed is associated with an increased risk, while one-year increase in walking speed is associated with a decreased risk of future incident knee replacement.

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INTRODUCTION

The utilization of knee replacements in the United States is projected to increase 673% between 2005 and 2030.(1) Knee replacements represent the largest Medicare expenditure for a single procedure with hospitals being reimbursed \$3.5 billion in fiscal year 2011.(2) Knee osteoarthritis (OA) is one of the most common indications for receiving a knee replacement and greater than 50% of knee OA patients are expected to receive a knee replacement in their lifetime under the current clinical guidelines.(3) While there are criteria to inform decisions about whether a patient is appropriate for a knee replacement, these criteria only indicate if a knee replacement would be appropriate based on a patient's current status.(4, 5) It would be beneficial to also have a reliable, clinically-accessible test to prognostically identify which patients are likely to receive a future knee replacement. This may enable a clinician to start a conversation earlier about the need for future knee replacement and encourage initiating and adhering to interventions that prevent/delay the need for knee replacement or optimize function prior to surgery to improve post-operative outcomes.(6-11)

While imaging outcomes may be prognostic for future knee replacement, they are not readily available to clinicians, which limits their clinical utility compared to more accessible assessments.(12) Habitual walking speed, which can be quickly assessed in a clinic, has been designated the "6th vital sign", because impaired walking speed may be a general indicator of declining health that predicts a range of important health outcomes: response to rehabilitation, lack of physical activity, functional dependence, frailty, falls, and mortality.(13) Walking speed is also a strong predictor of specific outcomes relevant to knee OA. Adults with slower walking speed have higher odds of developing knee OA over six years when compared to faster walkers.(14) Furthermore, adults with late-stage knee OA that elected to get a knee replacement presented with poorer performance on the Timed Up and Go test (i.e., slower walking) two years before opting for surgery compared to adults who did not receive a knee replacement.(15) Therefore, walking speed is a clinically accessible measure that is related to

OA-related outcomes throughout the disease process, and may serve as an optimal tool to assess the risk of future knee replacement.

While walking speed assessed at a single timepoint is prognostic of knee OA, a longitudinal change in walking speed has been theorized to provide a more sensitive measure of risk assessment.(16, 17) For example, when separating a cohort of participants by baseline walking speed, the adults who experienced a fast decline in walking speed were at higher risk of mortality regardless of whether they were considered a slow or fast walker at baseline.(16) Additionally, a one-year decline in walking speed (i.e., 0.1 m/s decline) in adults without knee OA was associated with an increased risk of developing radiographic knee OA over two years.(17) Decline in walking speed is also associated with worsening pre-radiographic structural pathology (i.e., increased bone marrow lesion and effusion volume) prior to the development of accelerated knee OA.(18) Thus, decline in walking speed may be a general indicator of declining health that may associate with increased risk for future knee replacement. However, it is unclear if longitudinal walking speed decline is associated with incident knee replacement in adults with and at risk for knee OA. Conversely, it is unknown if a longitudinal increase in walking speed is associated with a decreased risk of incident knee replacement.

Therefore, the primary purpose of this manuscript was to determine the extent to which a change in walking speed over one year was associated with receiving an incident knee replacement within the following year in adults with or at risk for knee OA. Additionally, we performed stratified analyses based on baseline walking speed status (fast walker: ≥ 1.22 m/s, slow walker: < 1.22 m/s (16)) to determine if the association between change in walking speed and incident knee replacement is different among those who started off walking slow or fast. This will help inform clinicians about whether change in walking speed will perform well at predicting knee replacement among everyone regardless of the person's initial walking speed. If walking speed decline is associated with an increased risk of future knee replacement, this may

allow for more targeted conservative treatment aimed at improving function and delaying time to knee replacement.

MATERIALS AND METHODS

Study Design and the Osteoarthritis Initiative

We conducted a longitudinal analysis using data from the first four years of the Osteoarthritis Initiative (OAI). The OAI is a multicenter (Memorial Hospital of Rhode Island, The Ohio State University, University of Maryland and Johns Hopkins University, and the University of Pittsburgh) cohort study that recruited 4,796 adults with or at risk for symptomatic knee osteoarthritis between February 2004 and May 2006.⁽¹⁹⁾ Institutional review boards at all of the OAI clinical sites and the OAI coordinating center (University of California, San Francisco) approved the OAI study. The OAI was approved and meets all criteria for ethical standards regarding human studies defined in the 1964 Declaration of Helsinki and all amendments made after. Institutional review boards at each clinical site and the coordinating center (University of California, San Francisco) approved the OAI study (approval number 10-00532). Participants provided informed consent prior to participation.

For this study, we created three observation periods that each consisted of a one-year change in walking speed and the following one-year period to determine incidence of knee replacement (Figure 1). Figure 1 demonstrates the exposure (i.e., walking speed change) and outcome (i.e., incident knee replacement) from each of the three observation periods. Participants could contribute data in all three observation periods depending on the availability of walking speed data and whether they experienced an incident knee replacement over the first four years of the OAI. The data from the three separate observation periods were combined to determine the overall association between one-year change in walking speed (exposure) and incident knee replacement during the following year (outcome) throughout the first four years of the OAI.

Participant Selection

We excluded participants that presented with a knee replacement prior to OAI baseline and those who received a knee replacement between the baseline and 12-month OAI visit. We included OAI participants with 20-meter walking speed data at two or more consecutive visits from the OAI baseline to the 36-month follow-up visit. Consecutive visits were needed to calculate one-year walking speed change in each of the three observation periods (i.e., baseline to 12-month, 12- to 24-month, 24-month to 36-month; Figure 1). Additionally, participants were excluded with missing covariate data.

Walking Speed Assessment

Walking speed was measured using the 20-meter walk test. Participants performed two trials of a timed 20-meter walk at their usual, comfortable walking speed.(16-18, 20) The participants began each trial in a standing position and an assessor used a stopwatch to start timing when the participant took their first step. An assessor stopped timing when the participant passed a cone positioned 20-meters away. To ensure that participants were not decelerating prior to the end of the test, participants were instructed to maintain their comfortable walking speed for three steps past the cone. Testing self-selected walking speed in adults with knee OA has high reliability (intraclass correlation coefficient > 0.93).(21) The time needed to complete the 20-meters was converted to walking speed (meters/second [m/s]) and averaged across two trials.

One-year change in 20-meter walk speed was calculated as the second year subtracted by the first year in each observation period (i.e., negative values indicate walking speed decline). We operationally defined one-year change in walking speed as either: 1) decline: ≤ -0.1 m/s change, 2) no change: between -0.1 and 0.1 m/s change, 3) increase: ≥ 0.1 m/s change. We selected a change of 0.1 m/s because this amount of change has been previously

reported as the minimally clinically important difference for change in walking speed,(22) is associated with the development of incident radiographic knee OA,(17) and is associated with worsening structural pathology prior to the onset of accelerated knee OA.(18) Our operational definition of walking speed change exceeds the established smallest detectable difference for decline in 20-meter walk speed (i.e., 0.07 m/s).(23)

Definition of Incident Knee Replacement

A participant was considered to have received an incident knee replacement if a knee replacement (i.e., partial or total; unilateral or bilateral) was self-reported or seen on an OAI study x-ray, and then centrally adjudicated by the OAI Coordinating Center.(24) Two adjudicators independently reviewed the medical records, and if disagreement a third physician adjudicator reviewed the medical records. Adults with a knee replacement from 0 to 12 months were removed from the study sample. We then indicated if a person received an incident knee replacement during one of three one-year intervals (12 to 24 months, 24 to 36 months, 36 to 48 months). If a participant received a knee replacement, they were censored from each subsequent period.

Operational Definition of Walking Speed Status Used for Stratified Analyses

To determine if baseline walking speed serves as an effect modifier of the association between change in walking speed and incident knee replacement, walking speed status was defined separately in each of the three observation periods based on a participant's walking speed during the first visit of each observation period (i.e., baseline walking speed). Similar to a previous manuscript associating change in walking speed with mortality in older adults,(16) we stratified the analyses using baseline walking speed as an effect modifier. We operationally defined walking speed status as: 1) slow: <1.22 m/s, or 2) fast: ≥ 1.22 m/s. A habitual walking speed of 1.22 m/s is a clinically relevant threshold because it is the speed needed to cross a

cross-walk during a traffic light change(25) and represents a minimum performance threshold that indicates the physical ability needed to walk >6,000 steps per day for adults with and at risk for knee OA.(20)

Potential Confounders

We extracted demographic data at the first visit for all observation periods from the public OAI data files: age, sex (female vs male), body mass index (BMI; kg/m²), WOMAC pain (0-20; greater score indicates worse pain), race (white versus non-white), and symptomatic knee OA status (defined by presence of both: radiographic evidence of knee OA = centrally-read Kellgren-Lawrence (KL) grade ≥ 2 on semi-flexed radiographs, AND presence of self-reported frequent pain = evaluated by pain, aching, or stiffness in or around each knee on most days for 1 month within the last year.(16)) (files: enrollees, version 23; allclinical##, version 0.2.2, 1.21, 3.2.1; KXR_SQ_BU, versions 0.6, 1.6, 3.5).

Statistical Analysis

We determined the association of a one-year change in walking speed (i.e., increase, decrease, or no change) and incident knee replacement in the following year over the first four years of the OAI with a repeated-measures relative risk estimation by modified Poisson regression with robust error.(26) Since each participant could contribute data from each of the three separate observation periods, the modified Poisson regression analysis adjusts for correlations within-person over time which allows for estimating the relative risk and confidence intervals by using robust error variances.(27) These relative risks determined how the risk of knee replacement in the increase and decrease in walking speed groups compared to the participants with no change in walking speed. To determine if baseline walking speed serves as an effect modifier of the association between change in walking speed and incident knee

replacement, we then conducted a stratified analysis using the same approach to assess this association in slow or fast walkers at the first visit of an observation period.

RESULTS

The final analysis included 11,311 total observations across 4,264 participants (3 observations, n=3358; 2 observations, n=331; 1 observation, n=575; Figure 2). Between the 12- and 48-month OAI visits, 115 (3%) adults received a knee replacement (i.e., 12-24 month: n=33, 24-36 month: n=42, 36-48 month: n=40). Table 1 highlights the demographics for the those with an increase, decrease, or no change in walking speed at the initial visit from the first observation period. In the year prior to knee replacement, 37% (42/115) of adults experienced a decline, 7% (8/115) experienced an increase, and 57% (65/115) experienced no change in walking speed (Table 2). In the observations that did not precede a knee replacement, 19% (2,111/11,196) experienced a decline, 18% (2,016/11,196) experienced an increase, and 63% (7,069/11,196) experienced no change in walking speed.

A decline in walking speed over one year is associated with a 104% increase in risk of incident knee replacement in the following year compared to a person with no change [adjusted relative risk (RR) 2.04; 95% confidence interval (CI): 1.40-2.98] (Table 2). An increase in walking speed over one year is associated with a 55% decrease in the risk of incident knee replacement in the following year compared to a person with no change in walking speed (RR=0.45; 95% CI: 0.22-0.93). Table 2 also includes the results of the unadjusted analyses that indicate similar associations between walking speed change and knee replacement.

When stratifying our cohort by baseline walking speed status, a decline in walking speed over one year in **slow walkers** was associated with a 210% increase in risk of knee replacement in the subsequent year compared to adults with no change (Table 2). Similarly, a decline in walking speed for **fast walkers** was associated with a 72% increase in risk of knee replacement in the subsequent year compared to adults with no change in walking speed (Table

2). The relative risks comparing risk of knee replacement between increase and no change in walking speed for the **slow** (RR=0.46; 95%CI: 0.17-1.19) and **fast** (RR=0.42; 95%CI: 0.13-1.35) walkers were considered non-significant since the 95% CIs crossed one. However, the magnitude of the relative risks for the **slow** and **fast** walkers was similar to the overall group, and the wide confidence intervals are likely due to the very small sample size of adults that increase their walking speed and received a knee replacement in the following year.

DISCUSSION

A decline in walking speed of 0.1 m/s over the course of one year is associated with a 104% increase in risk of receiving a knee replacement in the subsequent year when compared to adults that had no change or an increase in their walking speed, respectively. Conversely, an increase in walking speed decreased the risk of receiving a knee replacement in the subsequent year by 55% compared to someone with no change in walking speed. This association between change in walking speed and knee replacement was consistent for adults considered to be slow or fast walkers at their baseline visit of each observation period. These findings highlight that serial monitoring of walking speed is an accessible, clinically feasible test that may be included in a tool kit of tests to determine if a patient is at increased or decreased risk for knee replacement within the subsequent year. Improving our ability to identify people at an increased risk of knee replacement may allow for more targeted conservative treatment aimed at improving function and delaying time to knee replacement.(7)

The results of our walking speed status stratified analysis are in agreement with previous studies to highlight the importance of assessing change in walking speed, and not just baseline walking speed, as a sensitive marker for future poor outcomes.(16, 17) A previous study using a similar baseline walking speed stratification found that regardless of whether a person started as a slow or fast walker, adults within both groups that exhibited the fastest trajectory of walking speed decline were at greater risk for mortality within 8 years.(16) Similarly, we found that

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baseline walking speed is not an effect modifier of the association between walking speed change and knee replacement, because a decline in walking speed is associated with future knee replacement regardless of being a fast or slow walker at baseline. This indicates that even if a person is considered to have a “functional” baseline walking speed (i.e., >1.22 m/s),⁽²⁵⁾ a one-year decline in walking speed provides further insight into their health status and is associated with an increased risk of future knee replacement. While assessing walking speed at a single time point is an important indicator for future negative health outcomes,⁽¹³⁾ the sensitivity of a single baseline assessment of walking speed may be limited because it does not provide any indication of that individual’s history and how their speed is changing over time. In addition to the negative implications of a decline in walking speed, our results also indicate that an increase in one-year walking speed is associated with a decreased risk of knee replacement in the subsequent year compared to adults with no change in walking speed. Therefore, serial walking speed assessments may provide additional information to walking speed at a discrete time point, as this may help identify patients on a trajectory of walking speed decline prior to the occurrence of future adverse events.

This study highlights that walking speed change is associated with an incident knee replacement during the subsequent year in adults with and at risk for knee OA, but there are some limitations that need to be taken into consideration. Walking speed change was assessed over a 12-month period collected at two distinct timepoints and may not reflect the full extent of walking speed fluctuations that may occur throughout an entire year. However, this timing of the assessments may be easily translatable into a clinician’s assessment at annual follow-up visits. Since calculation of walking speed change requires two consecutive visits, we may have excluded participants with the greatest amount of physical limitations that were unable to complete walking speed assessments over two consecutive visits. However, since the design of our study includes three different observation periods, we were able to maximize the inclusion of participants throughout the first four years of the OAI. Due to the inclusion criteria of the OA, the

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results of this study should only be generalized to adults between the ages of 45-79 with knee OA or those matching age-specific criteria used by the OAI to identify adults at risk for knee OA.(19) While a decline in walking speed does increase the risk of a person receiving an incident knee replacement within the following year, the overall percentage of adults presenting with a decline in walking speed and receiving a knee replacement is small (Table 2). Since electing to undergo a knee replacement is influenced by many extraneous factors (e.g., race, geographic area, healthcare coverage), serial walking speed testing cannot serve as a singular test to estimate a person's risk for future knee replacement, but may be included in a larger tool kit to help accurately estimate a patient's risk of future knee replacement. Our results indicate that people with declining walking speed are more likely to receive a knee replacement compared to those with no change or an increase in walking speed, but our analyses cannot determine if declining walking speed is an indication of appropriateness for knee replacement. Future studies are needed to determine if adding in a serial walking speed test can improve current classification systems for determining the appropriateness of knee replacement.(4) While our results indicate that an association with knee replacement between both an increase and a decrease in walking speed, future studies are needed to determine if there is a causal relationship between interventions that create an increase in walking speed and preventing or delaying the time to knee replacement. The overall incidence of knee replacement in our study was low only 115 out of 4264 participants over our three observation periods. While the incidence of this procedure may be low, knee replacements place a high impact on individual patients and the healthcare system and being able to determine who is at risk is the first step to more targeted interventions.

In conclusion, a one-year decline in walking speed of 0.1 m/s is associated with a 104% increase in risk of knee replacement within the following year compared to people with no change in walking speed. Additionally, an increase in walking speed decreased the risk of receiving a knee replacement in the subsequent year by 55% compared to someone with no

change in walking speed. Walking speed decline represents a clinically accessible outcome that can easily be monitored annually to help identify adults at an increased risk of future knee replacement. Further studies are needed to determine if interventions that help prevent a decline or create an increase in walking speed will help to prolong the time to knee replacement.

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Figure 1. Defining the Observation Periods. An observation period consisted of a one-year change in walking speed and the following one-year period to determine incidence of knee replacement. There were three observation periods between the baseline and 48-month Osteoarthritis Initiative (OAI) visit. Specifically, in the 1st observation period, a participant's predictor variable was walking speed change from baseline to 12-month visit and their outcome was incident knee replacement between the 12- and 24-month visit. If a participant received a knee replacement, they were censored from each subsequent period. However, if a participant did not have an incident knee replacement during the 1st observation period, they could be included in the 2nd observation period with a new predictor (i.e., 12- to 24-month walking speed change) and outcome (i.e., incident knee replacement between the 24- and 36-month visit).

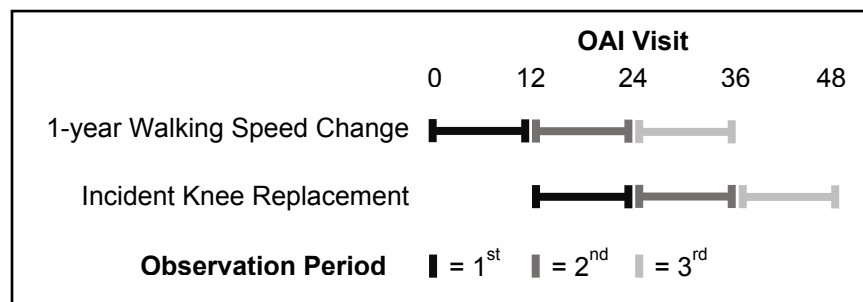


Figure 2. Flow of Participant Selection. Outlines the exclusion criteria where participants were excluded, and highlights the amount of observations per subject that led to the final participant and observation total included in the final analysis. Sx Knee OA Status = symptomatic knee osteoarthritis status.

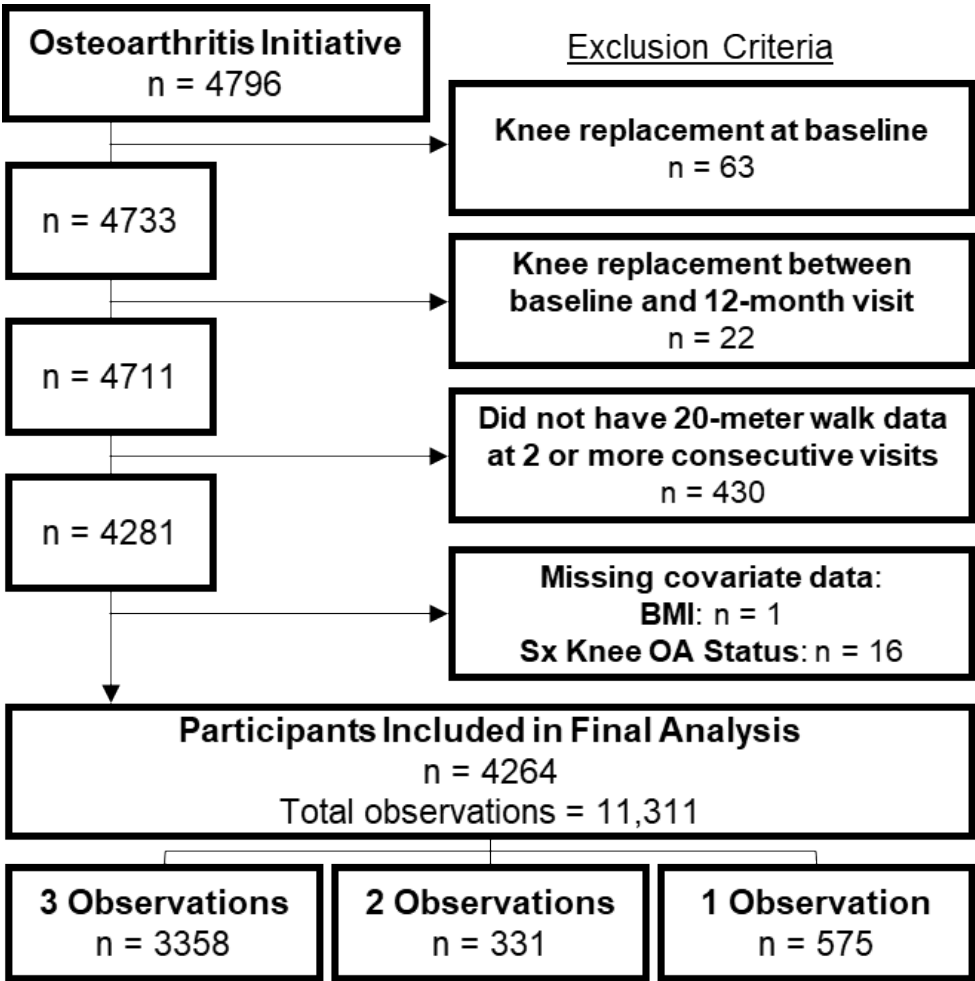


Table 1. Demographics of Groups with an Increase, Decrease, or No Change in Walking Speed

Demographic	One-year Change in Walking Speed*		
	No Change	Decrease	Increase
n	2531	777	956
Age (years)	61.4 (9.2)	61.4 (9.1)	60.3 (8.9)
Female, n (%)	1470 (58%)	476 (61%)	515 (54%)
Race [^] , n (%)	2098 (83%)	609 (78%)	746 (78%)
Body Mass Index (kg/m ²)	28.5 (4.7)	28.6 (4.9)	28.4 (4.8)
WOMAC Pain (0-20)	3.1 (3.4)	3.6 (3.8)	3.5 (3.9)
Baseline Walking Speed [%] (m/s)	1.33 (0.20)	1.43 (0.22)	1.24 (0.21)
Symptomatic Knee OA [#] , n (%)	757 (30%)	256 (33%)	272 (28%)

OA = osteoarthritis; *Walking speed defined as = decline: < -0.1 m/s change, no change: between -0.1 and 0.1 m/s change, increase: > 0.1 m/s change during a participant's first observation period. [^]Race: presented as percentage white; n = sample size; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index, higher score indicates greater pain; kg/m² = kilograms per meters squared. [%]Baseline walking speed = walking speed at the initial visit of a participant's first observation period. [#]Symptomatic knee OA defined by presence of both: radiographic evidence of knee OA = centrally-read Kellgren-Lawrence grade ≥ 2 on semi-flexed radiographs, AND presence of self-reported frequent pain = evaluated by pain, aching, or stiffness in or around each knee on most days for 1 month within the last year.

Table 2. Association between one-year change in walking speed and incident knee replacement

Incident Knee Replacement	1-year Walking Speed Change			Relative Risk Between Walking Speed Change Groups			
	No Change	Decrease	Increase	Increase vs No Change (REF)		Decrease vs No Change (REF)	
	n (%)	n (%)	n (%)	RR (95% CI)	aRR (95% CI)	RR (95% CI)	aRR (95% CI)
Overall							
No KR (REF)	7069 (63.1%)	2111 (18.9%)	2016 (18.0%)	0.43	0.45	2.15	2.04
Incident KR	65 (56.5%)	42 (36.5%)	8 (7.0%)	(0.21 - 0.90)	(0.22 - 0.93)	(1.46 - 3.16)	(1.40 - 2.98)
Slow Walkers							
No KR (REF)	1930 (62.6%)	313 (10.2%)	840 (27.3%)	0.43	0.46	3.96	3.10
Incident KR	27 (54.0%)	18 (36.0%)	5 (10.0%)	(0.16 - 1.11)	(0.17 - 1.19)	(2.20 - 7.11)	(1.71 - 5.62)
Fast Walkers							
No KR (REF)	5139 (63.3%)	1798 (22.2%)	1176 (14.5%)	0.35	0.42	1.80	1.72
Incident KR	38 (58.5%)	24 (36.9%)	3 (4.6%)	(0.11 - 1.12)	(0.13 - 1.35)	(1.08 - 2.99)	(1.05 - 2.80)

*Adjusted for age, BMI, sex, WOMAC knee pain, symptomatic knee OA, race; ^Walking speed change over one-year = no change: between -0.1 and 0.1 m/s change, decrease: ≤ -0.1 m/s change, increase: ≥ 0.1 m/s change; #walking speed status at the first visit in the observation period = slow walker: ≤ 1.22 m/s, fast walker: >1.22 m/s; RR = relative risk; CI = confidence interval; KR = knee replacement; % = percentage of walking speed change within knee replacement group