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Original Contribution

Mediation of the Associations of Physical Activity With Cardiovascular Events and Mortality by Diabetes in Older Mexican Americans

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Low physical activity (PA) among older adults increases the risk of cardiovascular disease (CVD) and mortality through metabolic disorders such as type 2 diabetes. We aimed to elucidate the extent to which diabetes mediates the effect of nonoccupational PA levels on CVD and mortality among older Mexican Americans. This study included 1,676 adults from the Sacramento Area Latino Study on Aging (1998–2007). We employed Cox proportional hazards regression models to investigate associations of PA level with all-cause mortality, fatal CVD, and nonfatal CVD events. Utilizing causal mediation analysis within a counterfactual framework, we decomposed the total effect of PA into natural indirect and direct effects. Over a median of 8 years of follow-up, low PA (<25th percentile) was associated with increased risks of all-cause mortality (hazard ratio (HR) = 1.36, 95% confidence interval (CI): 1.06, 1.75), fatal CVD (HR = 2.05, 95% CI: 1.42, 2.97), and nonfatal CVD events (HR = 1.67, 95% CI: 1.18, 2.37) in comparison with high PA (>75th percentile). Diabetes mediated 11.0%, 7.4%, and 5.2% of the total effect of PA on all-cause mortality, fatal CVD, and nonfatal CVD events, respectively. Our findings indicate that public health interventions targeting diabetes prevention and management would be a worthwhile strategy for preventing CVD and mortality among older Mexican Americans with insufficient PA levels.

cardiovascular disease; diabetes; mediation analysis; Mexican Americans; mortality; physical activity

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; MET, metabolic equivalent of task; PA, physical activity; SALSA, Sacramento Area Latino Study on Aging.

Physical inactivity is widely recognized as an important public health problem that increases risk of type 2 diabetes, cardiovascular disease (CVD), and mortality (1–5). Previous studies suggest that type 2 diabetes may be a mediator on the causal pathway from physical inactivity to these long-term adverse outcomes (6, 7). The prevalence of physical inactivity is higher among older adults (42%) and among Hispanics (40%) compared with younger adults (22%–33%) and non-Hispanic Whites (26%) (8). Moreover, a prior study using 3 national surveys showed that older Hispanics reported lower levels of physical activity (PA) than older non-Hispanic Whites (9), underscoring the importance of investigating the health burden of physical inactivity in this minority population.

According to the 2020 Diabetes Statistics Report, 1 in 10 people in the United States has diabetes, and the prevalence rises to 21.4% for those aged ≥65 years (10). While prescribing exercise is important for management of type 2 diabetes and subsequent long-term adverse outcomes (11), initiating and maintaining active lifestyle interventions in older adults is challenging due to multiple barriers, such as comorbidity, fatigue, pain, poor perceived health, and misconceptions about benefits of PA (12). In addition, in a recent study from the National Health and Nutrition Examination Survey (2016–2017), investigators reported that type 2 diabetes prevalence in Mexican Americans is nearly double that in non-Hispanic Whites (10, 13). Long-term health outcomes from diabetes may also differ by race/ethnicity—for example, prior studies found that diabetes showed weaker associations with CVD but stronger associations with mortality among Hispanics compared with non-Hispanic Whites (14, 15). Therefore, understanding the causal pathway from PA

to CVD and mortality through diabetes is crucial in order to prevent such long-term adverse outcomes in older Mexican Americans and reduce health disparities by race/ethnicity.

In the present study, using causal mediation analysis (16, 17), we aimed to investigate whether associations between nonoccupational PA and CVD (including stroke) or all-cause mortality are mediated by type 2 diabetes among older Mexican Americans. To address a potential role that sex hormones may have in modifying effects of PA on the cardiometabolic system (18, 19), we also investigated the mediation effects by sex. The distinction between direct and indirect effects provides valuable information about whether public health interventions targeting diabetes prevention and management would be beneficial for mitigating the overall risk of long-term adverse health outcomes among older Mexican Americans who are physically inactive.

METHODS

Study design and patients

We included participants with PA information from the Sacramento Area Latino Study on Aging (SALSA), a cohort study of community-dwelling older Mexican Americans in the Sacramento area of California. Eligibility criteria included 1) being 60 years of age or older at the time of enrollment in 1998–1999, 2) residing in a 6-county area in the Sacramento Valley region (Sacramento, Yolo, Sutter, Solano, San Joaquin, and Placer counties), and 3) self-identifying as Latino, Mexican, Central American, or Mexican American. Participants were contacted in 3 stages: 1) by mail, 2) by telephone, and 3) by door-to-door neighborhood enumeration. Participants who referred themselves were screened for eligibility, including residing in a targeted census tract and having a household on the sampling list. The overall response rate among those contacted was 85%. A total of 1,789 participants were initially enrolled, and they were followed with interviews and examinations in their homes every 12–15 months for up to 7 study visits through the end of 2007. Among the 1,789 participants, 1,676 had PA information at baseline. More details about sampling and study procedures have been provided elsewhere (20). All procedures described here were approved by the institutional review boards of the universities involved (University of California, San Francisco; University of California, Los Angeles; University of California, Davis; University of Michigan; and University of North Carolina).

MEASUREMENT OF VARIABLES

Physical activity

At baseline, participants were asked to report the average number of hours per week they spent in 18 different types of non-work-related activities that are common among older adults. Metabolic equivalents of task (METs) were assigned to each activity based on the Compendium of Physical Activities (21). This value was multiplied by the reported amount of time (hours/week) spent performing the activity (MET-hours/week). Cumulative PA measures were calculated to represent moderate- to vigorous-intensity PA levels by summing MET-hours/week values for 9 activities that require a 3-fold or greater increase over the metabolic rate achieved by sitting quietly (≥3 METs) (22): taking walks; walking around the neighborhood; dancing; hunting, camping, or boating; swimming or engaging in workouts; golfing or other moderate exercise; gardening or yard work; house repairs; and heavy housework (22, 23). Participants were then categorized into the following 3 groups according to their PA levels: low PA (<25th percentile; <20 MET-hours/week), medium PA (25th–75th percentiles; 20–97 MET-hours/week), and high PA (>75th percentile; >97 MET-hours/week).

Diabetes

We classified diabetes as fasting glucose level ≥7.0 mmol/L, use of antidiabetic medication, or self-report of a physician's diagnosis at baseline, as in previous studies (10, 24). Fasting glucose level was measured with the Cobas Mira Chemistry Analyzer (Roche Diagnostics Corporation, Indianapolis, Indiana). Medication use was assessed by means of a medicine cabinet inventory of prescription medicines.

Other covariates

At the baseline interview, participants reported their age, sex (male, female), educational level (0, 1–8, 9–12, or ≥13 years of education), country of birth (United States, other), marital status (single, married), tobacco smoking status (current, former, or never smoker), alcohol intake (frequent (daily) drinker, moderate (weekly) drinker, occasional (monthly) drinker, or rarely/never drinking), activities of daily living status, instrumental activities of daily living status, current employment status (yes, no), and type of lifetime occupation (nonmanual, manual, other). According to previous literature (25, 26), limitation in activities of daily living was defined on the basis of whether or not the participant report having difficulty with ≥1 activities. Similarly, limitation in instrumental activities of daily living was defined on the basis of whether or not the participant reported having difficulty with ≥3 activities (25, 26). Acculturation was assessed using the Geriatric Acculturation Ratings Scale for Mexican Americans, a modified version of the Acculturation Ratings Scale for Mexican Americans-II for use in older Latinos that consisted of 19 items assessing English and Spanish language and media use, childhood and current friendships, contact with Latin America, and dietary practices (27). Systolic and diastolic blood pressure measurements were made with an automatic digital blood pressure monitor while the participant was seated, and 2 measurements taken within a 10-minute interval were averaged. Hypertension was based on measured systolic blood pressure (≥140 mm Hg), diastolic blood pressure (≥90 mm Hg), self-report of a physician's diagnosis, and/or use of antihypertensive medication (28). Low-density lipoprotein cholesterol level was measured from a morning fasting serum sample using LDL Direct Liquid Select Cholesterol Reagent (catalog number 7120; Equal Diagnostics, Inc., Exton, Pennsylvania). Prescription statin use was also

self-reported. Body mass index (weight (kg)/height $(m)^2$) was calculated on the basis of the participant's measured height (tape measure) and weight (Tanita scale). Waist circumference was measured with a tape at the level of maximum indentation over the abdomen, following a standard protocol.

Ascertainment of outcomes

The primary outcome was all-cause mortality, with secondary outcomes being fatal and nonfatal CVD events (including stroke). Mortality data were ascertained through May 2010, using online obituary surveillance, review of the Social Security Death Index and the National Death Index, review of vital statistics data files from California, and interviews with family members. If participants were not identified as deceased, they were assumed to be alive and censored at the date of the last contact. Fatal CVD events were defined as death for which any of the following *International Classification of Diseases, Tenth Revision* (ICD-10) codes were mentioned anywhere on the death certificate: codes I20–I25 (ischemic heart disease), code I50 (heart failure), and code I63 or I64 (stroke). Nonfatal CVD events were ascertained by self-report at each visit and by phone call; that is, participants were asked whether a physician had diagnosed any of the following: myocardial infarction, angina, catheterization or coronary artery bypass grafting, stroke, heart failure, or atrial fibrillation. For analyses of nonfatal CVD events, 612 persons with a self-reported history of CVD at baseline were excluded to estimate effects of PA on primary CVD events.

Statistical analyses

Crude and multivariable Cox proportional hazards regression models were employed for estimating effects of categorical PA exposure (low, medium, high) on the risks of all-cause mortality, fatal CVD events, and nonfatal CVD events in separate models while adjusting for potential confounders. Missing data in each variable were replaced using multiple-imputation algorithms which included all of the above-mentioned covariates in the model (29). We first adjusted for age, sex, educational level, country of birth, and marital status (model 1). We then further adjusted for score on the Geriatric Acculturation Ratings Scale for Mexican Americans, smoking status, alcohol intake, activities of daily living, instrumental activities of daily living, current employment status, and type of lifetime occupation, in addition to the variables in model 1 (model 2). We also performed competing-risk analysis with the method proposed by Fine and Gray (30), considering the competing risks for fatal and nonfatal CVD events. In this competing-risk analysis, we estimated the subdistribution hazard by constructing risk sets that included both persons without any event and those who had competing events such as cancer-related mortality (30, 31).

In mediation analyses, we aimed to quantify the degree to which diabetes mediates the associations between PA and long-term outcomes, including all-cause mortality, fatal CVD, and nonfatal CVD events, adjusting for the potential confounders included in model 2 (see Web Figure 1, available at https://academic.oup.com/aje). We employed a marginal structural approach based on the counterfactual framework to estimate the natural direct and indirect effects (32, 33). The natural direct effect is the effect of PA on long-term outcomes via pathways that do not involve diabetes while diabetes status is allowed to vary according to determinants of diabetes, except PA. The natural indirect effect represents the effect of PA on long-term outcomes due to the effect that PA has on diabetes; that is, we estimate the hazard ratios for the counterfactual outcomes given a physically "active" status if diabetes status changed to what it would be given a physically "inactive" status. Robust 95% confidence intervals were estimated by repeating the analysis on 10,000 bootstrapped samples. The mediated proportion was computed as the log of the natural indirect effect divided by the log of the total effect. We included cross-product terms for exposure and mediator in the model, but there was no indication of an interaction. More detailed discussion and coding tutorials using R software are provided elsewhere (16).

Because previous studies have suggested that there is a difference in the effect of PA levels on long-term adverse outcomes by sex (3, 34, 35), we also conducted stratum-specific analyses to estimate the causal mediation effects of diabetes on the pathway between PA and long-term adverse outcomes according to sex. We also calculated *P* values for multiplicative interaction terms between PA level and sex for the total effects on long-term adverse outcomes.

We performed several sensitivity analyses. First, we additionally adjusted for other metabolic factors such as body mass index, waist circumference, hypertension, prescription statin use, and low-density lipoprotein cholesterol levels, which we did not include in the main model because we assumed that they are more likely to be mediators than confounders in the pathway from physical inactivity to CVD and mortality. Second, we reanalyzed the data using $\leq$8.3 MET-hours/week (i.e., 500 MET-minutes/week) as the cutoff for a low PA level based on the recommendation of the Physical Activity Guidelines for Americans (22, 36). Finally, we fitted Aalen's additive hazard models, which allowed us to estimate hazard differences without the assumption of proportionality (17). Using this model, we can estimate the actual number of additional events that provide insight into the potential public health interventions. Effect estimates presented here may be considered statistically significant if the 95% confidence interval does not include the null value.

Statistical analyses were conducted using Stata, version 15 (StataCorp LLC, College Station, Texas) and R, version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria). Sample syntax for each analysis is shown in the Web Appendix.

RESULTS

The mean age of participants was 70.3 years, and 41.7% were male (Table 1). PA levels were generally lower in participants with lower educational levels and those who rarely/never consumed alcohol but were higher among those in nonmanual occupations. The low-PA group exhibited the highest prevalences of diabetes, hypertension, obesity, pre-

Table 1. Baseline Clinical Characteristics of Participants According to Physical Activity Level, Sacramento Area Latino Study on Aging, 1998–2007

Variable	Total (n = 1,676)		Physical Activity Level, MET-hours/week					
			Low (<20) (n = 419)		Medium (20–97) (n = 838)		High (>97) (n = 419)	
	No.	%	No.	%	No.	%	No.	%
Male sex	699	41.7	127	30.3	356	42.5	216	51.6
Age, years[a]	70.3 (6.8)		71.4 (7.6)		70.1 (6.6)		69.8 (5.9)	
US birth	823	49.1	201	48.0	411	49.1	211	50.4
Education, years								
0	216	12.9	62	14.8	107	12.8	47	11.2
1–8	794	47.4	219	52.3	392	46.8	183	43.7
9–12	385	23.0	91	21.7	193	23.0	101	24.1
≥13	281	16.8	47	11.2	146	17.4	88	21.0
Married	979	58.4	223	53.2	492	58.7	264	63.0
Acculturation score[a,b]	22.0 (13.0)		20.7 (12.7)		21.9 (13.1)		23.4 (12.9)	
Tobacco smoking (all types)								
Current smoker	187	11.2	48	11.5	92	11.0	47	11.2
Former smoker	713	42.5	168	40.1	367	43.8	178	42.5
Never smoker	776	46.3	203	48.4	379	45.2	194	46.3
Alcohol consumption								
Frequent (daily)	147	8.8	27	6.4	73	8.7	47	11.2
Moderate (weekly)	181	10.8	25	6.0	89	10.6	67	16.0
Occasional (monthly)	153	9.1	24	5.7	86	10.3	43	10.3
Yearly/rarely/never	1,195	71.3	343	81.9	590	70.4	262	62.5
ADL difficulty[c]	200	11.9	112	26.7	66	7.9	22	5.3
IADL difficulty[d]	788	47.0	266	63.5	383	45.7	139	33.2
Lifetime occupation								
Nonmanual	362	21.6	68	16.2	194	23.2	100	23.9
Manual	1,000	59.7	241	57.5	496	59.2	263	62.8
Other	314	18.7	110	26.3	148	17.7	56	13.4
Currently employed	285	17.0	70	16.7	152	18.1	63	15.0
Statin use	141	8.4	41	9.8	68	8.1	32	7.6
LDL cholesterol level, mmol/L[a]	3.2 (0.9)		3.0 (0.9)		3.2 (0.9)		3.2 (0.9)	
Diabetes	542	32.3	166	39.6	256	30.6	120	28.6
Hypertension	1,136	67.8	309	73.8	547	65.3	280	66.8

Table continues

scription statin use, and history of CVD events. We found similar characteristics by PA level when we excluded participants with a history of CVD at baseline (Web Table 1).

The median duration of follow-up for all-cause mortality was 7.7 years (interquartile range, 4.7–8.4), during which 579 deaths were identified. A total of 263 fatal CVD events and 369 nonfatal CVD events were identified. All-cause mortality was higher in the low-PA group than in the high-PA group (hazard ratio (HR) = 1.36, 95% confidence interval (CI): 1.06, 1.75) after model 2 adjustments (Table 2). The low-PA group also experienced higher risks of both fatal CVD (HR = 2.05, 95% CI: 1.42, 2.97) and nonfatal CVD events (HR = 1.67, 95% CI: 1.18, 2.37) than the high-PA group. The medium-PA group showed higher risks of nonfatal CVD compared with the high-PA group (HR = 1.38, 95% CI: 1.03, 1.85). These results were not altered in the competing-risks survival regression model (Table 2, Web Table 2).

We estimated that diabetes mediated 11.0% of the effect of PA (low vs. high) on all-cause mortality (total effect:

Table 1. Continued

Variable	Total (n = 1,676)		Physical Activity Level, MET-hours/week					
			Low (<20) (n = 419)		Medium (20–97) (n = 838)		High (>97) (n = 419)	
	No.	%	No.	%	No.	%	No.	%
Body mass index[e]								
<25	324	19.3	83	19.8	158	18.9	83	19.8
25–29	628	37.5	135	32.2	326	38.9	167	39.9
≥30	724	43.2	201	48.0	354	42.2	169	40.3
Waist circumference, cm[a]	97.0 (13.3)		98.9 (13.8)		96.4 (13.4)		96.2 (12.5)	
Cardiovascular disease	612	36.5	187	44.6	300	35.8	125	29.8

Abbreviations: ADL, activities of daily living; IADL, instrumental activities of daily living; LDL, low-density lipoprotein; MET, metabolic equivalent of task.

[a] Values are expressed as mean (standard deviation).

[b] Acculturation was estimated using the Geriatric Acculturation Ratings Scale for Mexican Americans. Possible scores range from 0 to 56, and a lower score means the respondent is less acculturated (i.e., more Mexican-oriented).

[c] For estimation of ADL level, participants were asked whether they had any difficulty engaging in the following: walking, bathing, brushing hair and teeth, eating, putting clothes on, and moving from the bed to a chair. ADL difficulty was based on whether or not the participant reported having difficulty with ≥1 activities.

[d] For estimation of IADL level, participants were asked whether they had any difficulty engaging in the following: moving heavy objects, kneeling, lifting weights over 10 pounds (4.5 kg), extending arms above shoulders, getting up from kneeling, standing up from a chair, climbing stairs, writing, walking 0.25 mile (0.4 km), walking 10 steps, using a telephone, managing money, cooking, performing housework, and shopping. IADL difficulty was based on whether or not the participant reported having difficulty with ≥3 activities.

[e] Weight (kg)/height (m)^2.

HR = 1.36 (95% CI: 1.02, 1.81); indirect effect: HR = 1.04 (95% CI: 1.00, 1.09)) (Table 3). For fatal CVD events and nonfatal CVD events, we estimated that diabetes mediated 7.4% (total effect: HR = 2.05 (95% CI: 1.40, 3.09); indirect effect: HR = 1.05 (95% CI: 1.00, 1.14)) and 5.2% (total effect: HR = 1.67 (95% CI: 1.18, 2.45); indirect effect: HR = 1.03 (95% CI: 0.96, 1.10)) of the effect of PA, respectively. The mediation effects of diabetes on the association between PA (medium vs. high) and these outcomes were small, and the 95% confidence intervals included the null value. The results were qualitatively consistent when we additionally adjusted for metabolic factors (Web Table 3) and when we used the recommended PA levels as the cutoff point for defining low PA (Web Table 4).

In stratum-specific analyses, we estimated that diabetes mediated 55.8% of the effect of PA (low vs. high) on all-cause mortality for males, but there was no evidence of mediation among females (Figure 1, Web Table 5). For fatal and nonfatal CVD events separately, we estimated that diabetes mediated 22.9% and 22.1% of the effect for males but not females.

In Aalen's additive hazard model, we estimated that diabetes mediated 7.0% of the effect of PA on all-cause mortality among participants with low (vs. high) PA (total effect: 4,184 additional cases per 100,000 person-years; indirect effect: 292 additional cases per 100,000 person-years)) (Web Table 6). For fatal and nonfatal CVD events among those with low (vs. high) PA, we estimated that diabetes mediated 4.3% (total effect: 2,744 additional cases per 100,000 person-years; indirect effect: 118 additional cases per 100,000 person-years) and 2.2% (direct effect: 2,929 additional cases per 100,000 person-years; indirect effect: 63 additional cases per 100,000 person-years) of the effect, respectively.

DISCUSSION

In this population-based study of older Mexican Americans, diabetes mediated around 5%–10% of the association of physical inactivity with all-cause mortality, fatal CVD events, and nonfatal CVD events. Mediation effects of diabetes on these outcomes were much more prominent among males than among females.

To the best of our knowledge, this is the first study to have quantified the extent to which diabetes mediates the association of PA with all-cause mortality and CVD events in older Mexican Americans. Given the high prevalence of type 2 diabetes in this population and the challenges of prescribing exercise in older adults (12, 13), our findings underscore the importance of public health interventions for the prevention of type 2 diabetes and its long-term sequelae among physically inactive older Mexican Americans. While it is well known that PA influences risk of type 2 diabetes and CVD, including randomized controlled trials

Table 2. Incidence of All-Cause Mortality and Fatal and Nonfatal Cardiovascular Disease Events by Physical Activity Level, Sacramento Area Latino Study on Aging, 1998–2007

Outcome and Physical Activity Level, MET-hours/week	No. of Incident Cases	Total No. of Participants	Unadjusted Results		Model 1[a]		Model 2[b]	
			HR	95% CI	HR	95% CI	HR	95% CI
All-cause mortality								
High (>97)	115	419	1.00	Referent	1.00	Referent	1.00	Referent
Medium (20–97)	262	838	1.21	0.97, 1.51	1.25	1.00, 1.56	1.13	0.90, 1.41
Low (<20)	202	419	1.90	1.50, 2.39	1.85	1.46, 2.34	1.36	1.06, 1.75
P for trend[c]			<0.001		<0.001		0.03	
Fatal CVD event								
High (>97)	46	419	1.00	Referent	1.00	Referent	1.00	Referent
Medium (20–97)	111	838	1.25	0.89, 1.77	1.25	0.89, 1.77	1.07	0.75, 1.52
Low (<20)	106	419	2.88	2.03, 4.06	2.75	1.93, 3.91	2.05	1.42, 2.97
P for trend			<0.001		<0.001		0.001	
Nonfatal CVD event								
High (>97)	84	294	1.00	Referent	1.00	Referent	1.00	Referent
Medium (20–97)	192	538	1.52	1.15, 2.02	1.51	1.13, 2.00	1.38	1.03, 1.85
Low (<20)	93	232	1.97	1.42, 2.74	1.89	1.35, 2.64	1.67	1.18, 2.37
P for trend			<0.001		0.001		0.004	

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; MET, metabolic equivalent of task.

[a] Adjusted for age, sex, educational level, country of birth, and marital status.

[b] Adjusted for acculturation, smoking, alcohol intake, activities of daily living, instrumental activities of daily living, current employment status, and type of occupation, in addition to the variables in model 1.

[c] The median MET value was assigned for each physical activity category (low, 7 MET-hours/week; medium, 48.5 MET-hours/week; high, 147.5 MET-hours/week).

in older adults and meta-analyses (6, 7, 37–40), the extent to which type 2 diabetes mediates the association between PA and CVD has not yet been explored sufficiently. Previous studies suggesting that type 2 diabetes may mediate the association between PA and long-term adverse outcomes have approached this question by evaluating the change in the estimate with and without adjusting for the potential mediators (6, 7). However, such an approach does not always validly assess mediation, nor does it quantify this effect (17, 41). Here, we used more appropriate methods—that is, proportional and additive hazard models based on the counterfactual framework (16, 32).

The underlying mechanisms through which diabetes may mediate the association between PA and long-term adverse outcomes include improved energy balance, reduction of adiposity, and reduction of inflammation through high PA (42, 43). High PA also affects myosin phenotypic characteristics, increases mitochondrial activity and volume, and increases glucose transporter type 4 protein expression, which may reduce risk of type 2 diabetes through improved insulin sensitivity and subsequently reduce risk of CVD and mortality (44–46).

Consistent with prior studies (3, 34, 35), the estimated total effect of low PA on long-term outcomes was larger in females than in males, but the term for interaction between PA and sex was not statistically significant. In contrast, the proportion of the estimated effect of low PA on long-term adverse outcomes mediated by diabetes was larger in males than in females. In the San Antonio Heart Study, a cohort study of Mexican Americans aged 25–64 years, Monterrosa et al. (5) reported an association between low PA and type 2 diabetes incidence in males only. Biologically, higher PA is associated with lower levels of testosterone and estradiol in postmenopausal women but with higher testosterone levels in men (18, 19). The Mexican Americans in SALSA are older (ages 60–93 years) than participants in the previous studies, and PA might affect pathways involved in long-term adverse outcomes other than type 2 diabetes (e.g., endogenous levels of sex hormones); these might have larger contributions to the overall effect of PA on adverse health outcomes in females than in males. The observed sex discrepancy might also be associated with the PA health paradox—that is, high leisure-time PA decreases risks of CVD outcomes but high occupational PA increases this risk due to sustained inflammatory responses and 24-hour elevated heart rate (47). Because men are more likely to have manual occupations with higher PA demands than females, the benefits of engaging in nonoccupational PA for long-term adverse outcomes (especially the direct pathway that does not go through diabetes) might have been diluted by higher

Table 3. Direct and Indirect (Through Diabetes) Effects of Physical Activity Level on the Incidence of All-Cause Mortality and Fatal and Nonfatal Cardiovascular Disease Events (Hazard Ratio Scale), Sacramento Area Latino Study on Aging, 1998–2007[a]

Outcome and Physical Activity Level, MET-hours/week	Total Effect		Direct Effect		Indirect Effect		% Mediated[b]
	HR	95% CI	HR	95% CI	HR	95% CI	
All-cause mortality							
Medium (20–97) vs. high (>97)	1.13	0.89, 1.42	1.13	0.87, 1.42	1.00	0.97, 1.05	2.6
Low (<20) vs. high (>97)	1.36	1.02, 1.81	1.32	0.99, 1.77	1.04	1.00, 1.09	11.0
Fatal CVD events							
Medium (20–97) vs. high (>97)	1.07	0.75, 1.58	1.06	0.75, 1.56	1.00	0.95, 1.07	6.9
Low (<20) vs. high (>97)	2.05	1.40, 3.09	1.94	1.34, 2.96	1.05	1.00, 1.14	7.4
Nonfatal CVD events							
Medium (20–97) vs. high (>97)	1.38	1.02, 1.91	1.38	1.03, 1.92	1.00	0.97, 1.03	0.0
Low (<20) vs. high (>97)	1.67	1.18, 2.45	1.63	1.17, 2.41	1.03	0.96, 1.10	5.2

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio.

[a] Results were adjusted for age, sex, educational level, country of birth, marital status, acculturation, smoking, alcohol intake, activities of daily living, instrumental activities of daily living, current employment status, and type of occupation. We performed 10,000 iterations for bootstrapping to estimate 95% CIs.

[b] The percent mediated was calculated as log(indirect effect)/log(total effect) and therefore depended on both the total effect and the indirect effect.

occupational PA levels even after controlling for current employment status and type of occupation in men. Lastly, previous studies have found sex differences in type 2 diabetes due to obesity (42, 48, 49). In general, females have a stronger obesity-related risk of diabetes due to abdominal adiposity than males, and the impact of physical inactivity on this type of obesity is greater (48, 50, 51). Thus, future studies are needed to prospectively estimate mediating effects of both obesity and type 2 diabetes from PA to long-term adverse outcomes to elucidate mechanisms underlying sex differences (52).

The population-based longitudinal design of this study was a major strength, and it enabled us to analyze the incidence of long-term adverse outcomes over 10 years in an understudied older ethnic minority population. However, our study also had several limitations. First, while there is some evidence showing that low PA increases type 2 diabetes incidence (34, 49) and we assumed that self-reported PA reflected participants' long-term PA levels, we still have to consider the possibility of reverse causation (i.e., a diagnosis of diabetes might have affected PA levels). Persons diagnosed with diabetes would be expected to be encouraged by their health-care providers to increase their PA levels; thus, a reversal of temporality would be expected to induce a bias toward the null. Conversely, some persons diagnosed with diabetes a very long time ago may have become physically inactive due to complications of diabetes. Second, there was potential misclassification of the exposure, mediator, and outcomes. PA levels were estimated at baseline on the basis of self-reports, and no information was collected regarding trends in PA levels over the follow-up period. We classified the participants as having diabetes based on self-report, medication use, and fasting glucose level, as in previous studies (10, 24), but we lacked information on hemoglobin A_{1c} level, oral glucose tolerance testing, and the presence of diabetes-related antibodies (e.g., glutamic acid decarboxylase antibodies) at baseline. Relying on self-reporting of nonfatal CVD events could have introduced potential outcome misclassification. Moreover, mortality surveillance might have been less accurate after active follow-up ended in 2008. Even though misclassification was probably nondifferential with respect to exposure, the bias this may generate is not always bias toward the null in mediation analysis (17). Third, individuals had to survive to at least 60 years of age to participate in this study. Our estimates might have been affected by the nonenrollment of persons with disabilities and mortality among people with diabetes before age 60 years. Fourth, given that SALSA participants were residents of the Sacramento area, our findings may not be generalizable to older Mexican Americans elsewhere. Further multiregional studies with longitudinal measures of PA and diabetes are needed to overcome these limitations and to help better establish temporality.

Our model was based on the assumption that there are no other unmeasured confounders and no mediator-outcome confounders affected by exposure (17). However, for example, metabolic factors (e.g., obesity, hypertension, and dyslipidemia) might be affected by PA and also affect both diabetes status and long-term health outcomes. Therefore, we may overestimate the indirect effect if we do not control for metabolic factors, and on the other hand, we may underestimate the direct effect when we control for metabolic factors (i.e., adjust for factors that are intermediate in the pathway and not operating directly through diabetes). More-

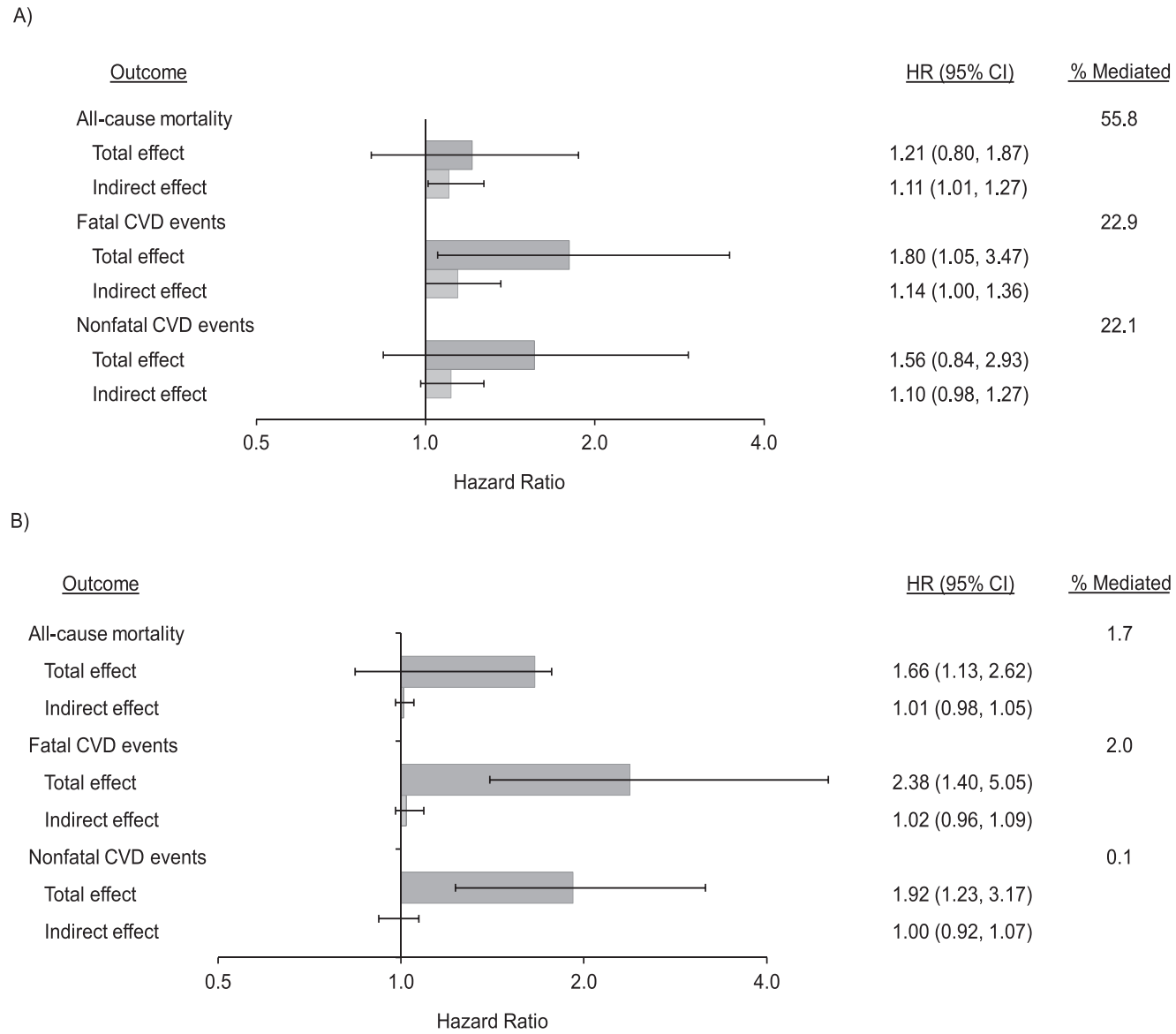

Figure 1. Decomposition of the effect of physical activity level (low vs. high) on the incidence of all-cause mortality, fatal cardiovascular disease (CVD), and nonfatal CVD events via diabetes, by sex, Sacramento Area Latino Study on Aging, 1998–2007. A) men; B) women. Hazard ratios (HRs) were adjusted for age, sex, educational level, country of birth, marital status, acculturation, smoking, alcohol intake, activities of daily living, instrumental activities of daily living, current employment status, and type of occupation. We performed 10,000 iterations for bootstrapping to estimate 95% confidence intervals (CIs) for the total effect and the indirect effect (through diabetes). The *x*-axis is shown on the log scale. The percent mediated was calculated as log(indirect effect)/log(total effect).

over, if there is unmeasured confounding between metabolic factors and outcomes, controlling for such metabolic factors could induce collider-stratification bias (53). However, we found qualitatively consistent results when we adjusted for metabolic factors, indicating that these potential biases did not change our main findings substantially. As we mentioned above, more advanced mediation analysis with multiple mediators would be helpful to fully address this issue in the future but would require larger samples (52).

In conclusion, the present study suggested that diabetes mediates the estimated effects of physical inactivity on long-term adverse outcomes among older Mexican Americans, particularly men. Given the rapidly growing older adult population with a high prevalence of diabetes and the challenges of prescribing exercise in older adults, our findings suggest that public health interventions targeting diabetes prevention and management (e.g., active diabetes screening programs focusing on physically inactive older adults)

would be worthwhile strategies for preventing long-term adverse outcomes in older Mexican Americans.

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